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Section for the Study of Disease in Children

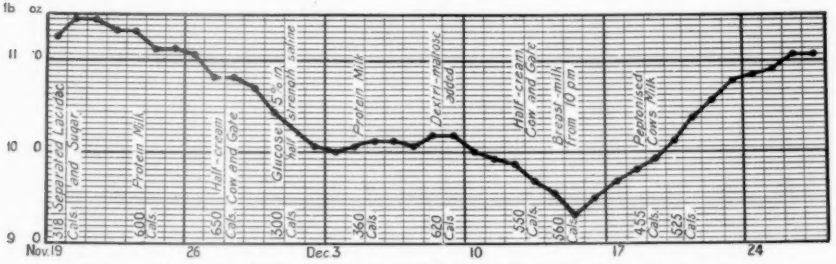
President—Cecil P. G. Wakeley, F.R.C.S.

[*January* 26, 1940]

Marasmus treated by Breast-Milk. — E. Hinden, M.B., M.R.C.P. (by permission of Dr. Basil Hood).

Terence R., aged 10 weeks, admitted to St. Charles' Hospital on October 25, 1939, with gastro-enteritis. Weight at birth 7½ lb., on admission 10 lb. 12 oz. Fair progress at first, in spite of two relapses; weight reached 11 lb. 7 oz. on November 20. After this he had two more severe relapses, his weight steadily declining. In the first week of December it became clear that his failure to gain was due to a failure to digest the food given him; there was no watery diarrhœa, but the motions appeared to contain all the solid constituents of the milk, no matter how it had been modified.

By mid-December his weight had sunk to 9 lb. 5 oz., and his condition appeared desperate. A small blood transfusion was given, without apparent benefit. It



Terence R. The chart shows the weight, the feeds and their caloric values.

was then suggested that breast-milk might be digested although cow's milk was not. Telephone calls to Queen Charlotte's and to two neighbouring L.C.C. hospitals failed to procure breast-milk, so as a last resort the B.B.C. was asked to broadcast an appeal. This was done at 9.15 p.m. on December 14. Within ten minutes 12 mothers were at the hospital, a thirteenth came about ten minutes later, and that evening some 60 others had telephoned offering their assistance. Not all of these were accepted; actually some 30 of them gave milk, all of which was pooled and given in three-hourly feeds of 4 oz. each to the child. The milk so provided—84 oz.—was enough for three and a half days, during which he gained 8 oz., the first gain for three and a half weeks. He was then fed on peptonized dilute cow's milk, gaining 17 oz. in the next week, and has not looked back.

Pfeiffer's Meningitis.—DONALD PATERSON, M.D.

Roy A., aged 1 year and 6 months.

30.11.39: Admitted to Westminster Hospital suffering from drowsiness and irritability of 4 days' duration. The illness began by the parents' noticing that the child was flushed and breathing hard, and putting his hand to his head. He became lethargic, did not recognize anyone, and was unable to sleep. When touched he gave a peculiar cry.

On examination.—Temperature 102° F., pulse 136, respirations 25. Flushed face. He would lie with eyes open. No photophobia. Neck very stiff. No head retraction. Tongue clean. Tonsils a little enlarged. Ears, eyes, heart, lungs, and abdomen normal. Kernig's sign positive. Brudzinski's sign positive. W.B.C. 15,200 per c.mm. Urine: No albumin or sugar. Tuberculin patch test negative.

Treated with sulphanilamide up to 7.12.39, then given M & B 693 until 10.12.39. Sulphanilamide was again given from December 11 to 16, and an intramuscular injection of M & B 693 on 24.12.39. The dose was gradually increased up to 30.12.39, then gradually decreased, and the treatment was discontinued on 1.1.40. The child did not seem to respond very well.

Over all this period he had a remittent temperature and the pulse-rate remained high, reaching 170 on occasions. On 13.1.40 the temperature became normal. Since then there have been remittent but lower temperatures.

21.12.39: Blood transfusion given. Skiagram of chest, 8.1.40: No focus of tuberculosis.

Lumbar punctures.—30.11.39: Fluid turbid, increased pressure. Spontaneous coagulum. No organisms. Cells: 56 polymorphs, 53 monocytes per c.mm. Chlorides 627 mgm. %. 1.12.39: Fluid cloudy. Spontaneous coagulum. No organisms. Culture negative. 2.12.39: Cells: 74 polymorphs, 92 monocytes per c.mm. Total protein 0·085%. Chlorides 603 mgm. %. Culture negative. 4.12.39: 740 polymorphs, 260 monocytes per c.mm. No organisms.

Further examinations up to 30.12.39 showed no marked change in the fluid.

11.1.40: Fluid cloudy. Spontaneous coagulum. Cells 290, mostly monocytes. Total protein 0·125%. Smear showed pus and Gram-negative bacilli.

16.1.40: Smear again showed pus and Gram-negative bacilli. Culture gave Gram-negative bacilli of the hæmophilus variety. 22.1.40: Culture again showed similar organisms.

Anæmia with Splenomegaly.—DONALD PATERSON, M.D.

Girl, aged 6 years, admitted to hospital on 22.1.40.

From birth the abdomen had appeared abnormally large. At the age of 2 she had a moderately severe bout of jaundice, which after an acute phase of two weeks had persisted in a slight degree ever since.

In February 1939 she had three severe hæmatemeses in a period of twelve hours. Subsequent to this she gradually put on weight and appeared quite well on a normal diet until November 1939, when she had three further hæmatemeses in a period of thirty-six hours. The vomit consisted of changed blood on all occasions. After admission to hospital she improved until the week after Christmas, when she had three further hæmatemeses.

Bowels usually required aperients. The motions towards the end of last summer were very dark.

Family history.—Mother has mild diabetes. Father gave history of peptic ulcer.

On examination.—Several carious teeth. Abdomen distended. Fluid thrill. Enlarged spleen and liver. No enlarged glands felt anywhere in the body. Temperature and pulse have been normal except immediately after the hæmatemeses.

Urine showed no trace of bile.

Blood-count (approx.): R.B.C. 2,000,000; Hb. 40%; C.I. 1; W.B.C. 8,000. Differential count normal.

Tuberculin patch test negative.

Barium meal: X-rays showed the pyloric portion of the stomach as a digital process beneath a grossly distended fundus.

Dr. HERBERT LEVY said he had seen cases of this syndrome due to chronic thrombophlebitis of the splenic vein. In such a case the great danger of pulmonary embolus following splenectomy could now be materially reduced by heparinizing the patient for about a week. If laparotomy should reveal thrombosis of other tributaries of the portal vein, or of this vein itself, or a cirrhosis of the liver, the condition might perhaps be somewhat improved by an omentopexy which, with the technique of some surgeons at least, seems to be of greater value than is generally believed.

After this case was shown the spleen was removed and a section showed the typical picture seen in Banti's disease. The anæmia rapidly improved and the child was discharged to convalescent home with a hæmoglobin of 80%.

Tetanus Secondary to a Nasal Lesion.—DONALD PATERSON, M.D.

History.—A male aged 2½ years was admitted to the Westminster Hospital (Children's Department) on November 16, 1939. Apparently there had been a convulsion on November 12, and further ones had occurred each night from that date.

On examination (November 16).—A left facial paralysis was present, but the child was clear mentally, and showed no signs of hemiplegia. He could stand on his legs, and could take his food. It was thought at that time that there must have been some cerebral damage at birth, or a recent vascular lesion, and that the fits were epileptic in character. A lumbar puncture showed the fluid to be clear and normal, and under no pressure.

November 19 the temperature began to rise, and by November 20 well-marked trismus was seen, and the child now resembled a typical tetanus. At any attempt to handle him a spasm was provoked, with marked opisthotonus.

Treatment.—Altogether 320,000 units of antitetanic serum were given intramuscularly, divided between the first two days, with an additional 40,000 units on November 24. Avertin, 0·1 c.c. per kgm. of body-weight, was administered rectally on 10 different occasions, sometimes two doses being given in twenty-four hours, and dependent on the severity of the spasms. This was administered over a period of twelve days, and during that period he was nasally fed entirely.

Course of disease.—When the nasal feeding was commenced, it was found that the posterior part of the nares on the left side (the side of the facial paralysis) was blocked with three lumps of coal as large as peas. These were removed and cultured, but no tetanus organisms were grown. He recovered in just under four weeks from the onset of the illness. The clinical picture of tetanus did not show itself until the eighth day after the initial convulsion.

Comment.—One of Cole's [1] cases, a child aged 3 years, commenced her illness with a right facial weakness, after a convulsion. In our case there is no history of trauma in any other part of the body, and the comparatively large pieces of coal inserted into the left nostril, and followed by left facial paralysis, seem suggestive to us as a source of infection.

Conclusions.—(1) A large dose of antitetanic serum (320,000 units) was given with apparent benefit. (2) Avertin appeared to give the child real relief, and made feeding possible. (3) The period of onset, that is the time from the appearance of the first symptom to the occurrence of the first regular reflex spasm, was in our case eight days, and the outcome conformed with the dictum laid down by Cole that the longer the period of onset, the better the prognosis.

Reference.—1 COLE, L. (1935), The Treatment of Tetanus, *Quart. J. Med.*, New Series, **4**, No. 15, 295.

[*February* 23, 1940]

DISCUSSION ON THE PROBLEMS OF THE EVACUEE CHILD

Dr. H. C. Cameron: The momentous and unprecedented decision to evacuate the school population together with the children under school age accompanied by their mothers, under a voluntary scheme, was undertaken in anticipation of and under fear of continuous and devastating attacks from the air. That these anticipations have not as yet been fulfilled has meant that so far a scheme devised to meet such terrible contingencies, a scheme which at the best could prove acceptable only as an alternative to danger and devastation such as this country has never experienced, has been, as it were, left in the air. The place of security and safety in the country, with all its drawbacks, difficulties and deprivations, has had to bear comparison not with homes endangered or devastated, but with the familiar, ordinary life which is so far still enjoyed in safety in our cities. That after six months of such daily comparison most of the mothers and at least half of the children have returned to their homes is not surprising. How greatly this reflux has added to the difficulties of adjustment between the health authorities of the evacuating areas and of the reception areas I shall discuss later.

The evacuation scheme was carried out by the combined action of the Ministry of Education, which dealt with the children of school age, and the Ministry of Health, which dealt with the mothers and the children under school age. The difficulties inherent in the task were enormous and were added to by the nature of the relationship in which the Ministry of Health stands to the many local health authorities throughout the country. A main function of the Ministry is the control and co-ordination of schemes for child health originating locally. It is a body which exists to advise. It is in no sense a legislating power and it cannot readily enforce compliance upon the local authorities by dictation or insistence, except in so far as it is dealing with specific parliamentary enactments. It encourages the local authorities, facilitates, criticizes, and perhaps aids in the financing of their schemes. To an outsider there appears to be nothing bureaucratic in the Ministry of Health. It exists to place all its resources at the disposal of the various public health authorities in town and country, but the authority remains with them.

With a public health organization so conceived and so existing, the task of the Ministry became one of great difficulty when it was called upon in a day, under a voluntary scheme, voluntary, that is, both as regards the evacuated population and those who received them, to transfer the child population of cities with their elaborate and expensive health services into rural areas with slender resources, exiguous staffs, and comparatively rudimentary health services. The rural areas had to be encouraged and assisted to inaugurate and extend services and to arrange for the reception of such of the medical and nursing staff as could be spared from the evacuating area and the evacuating area was willing to relinquish. The increased expenditure incurred by the reception area had to be met by an agreed contribution from the evacuating area or by special grant. The scheme for evacuation does not, and in the present constitution of the Public Health Service could not, lay down even minimal requirements in respect of what each rural health authority must supply and create.

The scheme starts with the assumption that the only possible way to provide shelter for such great numbers of children was by billeting. They were so numerous that no plan was considered whereby they might be received into a communal life in quarters previously prepared for their reception. They must occupy any room in any house which happened to be empty, and their mothers had to be content to surrender their children to the care and protection of its unknown owner. In my view it is beyond question that the year since Munich might have been profitably employed in many areas to perfect arrangements in villages and towns whereby each

undertook the communal reception of its assessed quota of children in buildings selected or in huts erected for the purpose. Here is a letter which I wrote and sent to *The Times* soon after Munich. Although perhaps in the light of experience I might to-day word it a little differently, it still embodies what I believe would have been the wiser plan, at any rate in many parts of the country.

> "Sir," I wrote, "my work makes me view with intense concern the proposal to billet the school population indiscriminately among persons who may or may not have understanding of children and their control. I have in mind not only the certainty of outbreaks of illness of all sorts. I am thinking also of the risks of moral contamination from child to child. Taken in the bulk the possibilities of disastrous happenings under billeting would be enormous and a risk that no mother should be asked to run. In the supervised, occupied, communal life of schools and camps, dangers of this sort are reduced to a minimum. Children should be sent not to this or that room which may be found empty in a household perhaps profoundly ignorant of children's ways and needs, but to an environment which provides security, supervision and occupation.
>
> Cannot such an aim be achieved? If every township or village is given its quota of children is it beyond the power of such a community, aided by Government funds, to make the necessary provision? A model unit for fifty children could be repeated in any multiple, a building of one room designed for the purpose, with alternative arrangements for heating, cooking, bathing and sanitation according to the facilities available at the site. The country community would make it its business to staff the unit under the direction of one or more resident school teachers or voluntary workers and generally to join in promoting the welfare and comfort of the children. In peace-time such a building might serve for some weeks in the summer as a holiday home for the same children from the same school. The children would not then be evacuated into the unknown but into the well-known holiday quarters among friends. During the rest of the year the country community would have the benefit of the building to serve as an active centre of social life. Five thousand such voluntary associations would go far to meet the difficulty so far as London is concerned. Accommodation, additional to that provided by the centre, could be found in homes specially selected beforehand or in dormitories in larger houses under the care of a resident guardian. Children boarded out in this way would also be under the control of the central organization. They would be like day boys in a boarding school, an integral part of the whole. Finally a medical service would be necessary with mobile units of doctors trained in pædiatrics and in infectious fevers as well as a sufficiency of improvised hospitals."

This last suggestion brings me to remark on what is perhaps the most notable omission in the scheme, the absence of any plan to make use of the services of men and women specially trained in pædiatrics and their nursing staffs. The Emergency Medical Service made no such mistake and saw to it that special experience of all sorts—neurological, orthopædic, otorhino-laryngological, psychiatric, and so forth—was organized, available, and in the Service. It is true that as matters have gone these expert services have not been required. The casualties have not occurred. But for the million evacuated children no similar arrangements were made to mobilize the special pædiatric experience of the country. This curious lack of appreciation of the all-important services which pædiatricians and their nursing staffs alone can render is no new thing in this country. The work of the Ministry of Health is and must be largely concerned with children. The vast expenditure upon schemes of infant welfare, for example, has, in my view, been less fruitful than it might have been, because such schemes have seldom been controlled by men or women of extensive pædiatric experience. An assistant M.O.H., hoping to create for himself a career in

Public Health work, may for a time become the officer in charge of infant welfare, but I doubt if he thereby becomes a pædiatrician or what one might call pædiatrically minded.

When it was realized that all pædiatric special knowledge and experience, other than that already in the Public Health Service, was to be excluded from service among the evacuated children, on the initiation of Professor Charles McNeil, Dr. Donald Paterson, Sir Frederic Still, and others, a deputation approached the Ministry with a scheme to extricate pædiatricians and the children's nursing service from the Emergency Medical Service in which both had become firmly embedded and to constitute a special pædiatric service in the receiving areas. The recommendations, if accepted, involved the co-operation of pædiatric clinicians with no training in Public Health administration and Public Health officers of administrative experience, but with small clinical experience. It demanded just that co-operation, the absence of which in my view has been the weak spot in much admirably planned Public Health work for children. Although the Ministry was sympathetic it is not surprising that the attempt to establish for the first time such novel co-operation upon the scale suggested during the turmoil and difficulties of evacuation has been judged impossible. The Ministry may well have felt that it would be hard at the present time to induce local health authorities to initiate such an extension of their work as had never been contemplated in peace-time. Something, however, has been done to remedy the initial mistake. In each of the sectors for London a pædiatrician has been placed in charge of a pædiatric unit in one of the E.M.S. hospitals, with a number of beds which is capable of expansion if need be. It is hoped that similar arrangements will soon be completed throughout the country. The pædiatrician in charge will be in close touch with the Medical Officer of Health and with the Regional representative of the Ministry of Health, and will be available for consultation on all problems which may arise. It may be that by this somewhat loose association as much may be achieved as by a more formal scheme. Meanwhile many highly trained pædiatricians are still employed in the E.M.S. on duties other than pædiatric. It is to be hoped that more will gradually be moved to posts where their pædiatric training may be of use although they still remain in the service of the E.M.S.

The situation has been complicated, both for the Public Health authorities and for the Education authorities, by the drift back to the cities. The reflux has been gradual and its extent unpredictable, so that it is a matter of increasing difficulty to determine in any evacuating area what proportion of the staff, educational, medical and nursing, can be freed for service in the reception area and what proportion must be retained to meet the needs of the gradually increasing population of returning children. We shall hear in this discussion how far these adjustments have been achieved and how far there has been a deadlock. There are very many services which the children enjoyed in the evacuating areas which one would wish to follow them into the country. School inspection, dental care, the distribution of milk, infant welfare and child guidance, immunization against diphtheria. How far have these been provided in part or in whole ? How far are children, who have been used to receiving only pasteurized milk, being given raw milk and with what result ? Have the physically defective children who were under continuous expert care in hospital out-patient departments been separated from that supervision which is so necessary for them ? What provision in general has been made for sickness among the evacuated population ? How has the arrangement by which the foster mother for the time being may call in a general practitioner worked in practice ? Is the establishment of sick bays and small auxiliary hospitals to which children suffering from minor complaints can be transferred an effective and safe provision ? Is the accommodation for serious illness in the voluntary hospitals in the receiving areas and in the E.M.S. hospitals sufficient, and is it staffed and nursed satisfactorily ? To what extent has it been possible to improvise an out-patient service for the children, a very necessary

provision if children are not to be sent back to London hospitals for consultation or advice.

Lastly, there is the response of the individual child to any scheme of evacuation which involves his transference from one home to another. The dependence of the child's conduct upon his management and the circumstances of his home life is so intimate that any scheme of evacuation which involves such a change is bound to be productive of many problems of conduct and behaviour. If a child from a poor home is evacuated to a well-to-do home it is inevitable that he should make comparisons between life as he knew it and life as he finds it in his new surroundings. One father, after one of his elder children had returned home for Christmas from such surroundings, politely but firmly insisted on removing all the others. He did not want, he said, his children made gentry and snobs, and demanding things that he and his wife could not supply. What chance has an overdriven mother in a poor quarter of retaining her children's affections against the assault of some educated and fascinating woman who devotes her time to her evacuated guests, reading aloud to them perhaps by the hour before it is time for a dainty supper and a warm bath ? Unless we are to face a crop of new difficulties when the time comes for these children to return home, it would be well to arrange that in such cases there should be interposed a prolonged stay in camp or school to eliminate a little the sharpness of the contrast. Again in prim, well-ordered households, where the furniture has a high polish, we hear much of outbursts of destructive violence, the result of too-persistent repression. As might have been anticipated, enuresis has been a veritable flood. The reactions of children to strange surroundings and different management may well be examined and recorded, whether these reactions are favourable or the reverse.

Dr. E. M. Creak : In considering the psychological aspect of an evacuation scheme involving, broadly speaking, all the children of a district, one is driven to consider how far such a scheme can ever be made workable in the bulk of cases, since the children mostly concerned are those who rarely leave their homes and parents except in cases of sickness or other gross disturbances in family life.

Fortunately, the stable child is amazingly adaptable, otherwise the incidence of problems would be far greater than it is, but there is a tendency to infer that the benefits of life in the country will be such that the interference with routine can be discounted. A certain proportion of problems is inevitable, and in no sense reflects on either the children or the foster-parents concerned.

The problem is a threefold one. It concerns the foster-parent and family who may have been unwillingly compelled to accept an unwanted responsibility ; the parents left at home, who now find themselves without what is normally the major concern in their lives, and the children themselves, who are in a sense uprooted and removed from their usual source of love and support.

Should there be a sense of grievance in any of these three spheres, then the likelihood of achieving an adjusted settlement in the new conditions is quite remote.

Obviously much can be done by wisdom in the choice of billets, but in undertaking a very small scheme of foster-home placement for problem children some years ago, I realized that the naturally good foster-mothers were more difficult to find than homes which, in the material sense, were satisfactory. The capacity to maintain a fair balance between the claims of her own children and those of the foster-child, without making either feel unwanted, while at the same time allowing a friendly contact between the foster-child and his own parents, calls for qualities of exceptional good humour and insight. These were not always found, even in specially chosen foster-parents who had offered themselves for the task of accepting a difficult child for boarding out. Where such a situation is forced on a busy mother, her inability to

cope with every detail is not to be wondered at, and the problem of the psychologically unsuitable foster-parent is perhaps receiving less attention than it deserves.

A number of cases have been seen in which mild or even severe neuroses and psychoses have arisen in parents who are forlorn without their children. The disturbing influence of such parents is so natural a thing that it must account for their tendency to criticize the arrangements in a great many cases where otherwise the chances of settling down were good. Where the parents react in this way, they have probably been obtaining more emotional satisfaction from the children than they realized, so that a correspondingly severe deprivation may also be felt by the child, who would be unaware of why he so much missed his mother.

Not a few children, who have been involved in such a close attachment, have expressed the idea that, in the event of air raids, they would rather not leave their parents in danger, but prefer to face it with them—a not unnatural point of view. This is in line with the very common anxiety, expressed in terrifying fantasies and dreams of the parents being killed, seen in the night-fears of the so-called "over-protected child". How far such fears may also represent the unconscious wishes of the child to get rid of the hampering parent, however drastically, is a theoretical point beyond the scope of this discussion, but it is significant that such children often show excessive guilt reactions in relation to separations from their parents which may occur in the ordinary way.

In attempting even a superficial analysis of evacuation problems, a distinction must be drawn between the problem child who happens to get evacuated, and the reactive case, that of the stable child who would have remained normal at home, but who develops a problem directly in relation to evacuation. In between come those relatively unstable children who maintain a good adjustment at home, which breaks down under the strain imposed by evacuation to unfamiliar surroundings.

It is interesting to see the conditions to which children adjust quite readily, and some to which they are unexpectedly sensitive. The average child tolerates mess, untidiness, overcrowding, and irregular hours and unusual foods with considerable ease. It is usually the parents who, in these circumstances, will criticize. A 10-year-old boy from a good-class home, attending a secondary school, was found by his mother, in the recent cold weather, to have been regularly put to bed by his foster-mother in his school blazer, with three of her own old dresses on the bed. This foster-family never had anything but tinned milk but the evacuee neither objected to the sweet milk nor the warm, stuffy bed. How far do such experiences, obviously not in themselves desirable, really harm a child accustomed to better things? This situation arose simply from a difference in standards which resulted in a drop for the evacuee. On the other hand, a relatively wealthy and commodious billet, in which a mother and three children were given a nursery wing of a large house, but a hot meal only three times a week, resulted in considerable friction and dissatisfaction.

My own direct contact with evacuation problems has unfortunately been limited to a few returned cases, referred to the Maudsley Hospital Child Guidance Clinic, and to a visit which I was able to make to Huntingdon, where there and in the county, a co-ordinated scheme is in operation for dealing with problems as they arise.

Bowlby, Winnicott, and Rickman (1939) have suggested that in the nursery school group, broadly of under five, separation imposes a great strain on the child, who will be in the process of building up fundamental relationships with his parents, which will become the focusing point of all his subsequent emotional adjustments. At the same time the young child is, psychologically speaking, not fully weaned from parental care in relation to all his daily activities, such as dressing, eating, elimination, and locomotion, and he will fail to establish certain essential controls in these respects if he is impersonally cared for by a succession of people to whom he has no particular attachment. This may account for the frequency during the first weeks at an evacuated nursery school of a regression in habits, particularly to fæcal incontinence.

The "accidents" included many instances of smearing and playing with fæces, while at the same time the children were frightened, and inhibited. They showed their fear, particularly in relation to the open spaces and tall trees, many not venturing out at first. In this particular school, a progressive improvement has now been observed in the children's capacity to notice and appreciate natural things, and in their comments on them. They ask to see the moon and the stars every night when going to bed, and run freely out of doors.

Among the older group, the more severe reactions have not differed from the problems commonly seen in child guidance clinics. Perhaps owing to the frequency of some kind of "dormitory" arrangement, sleep disorders seemed to be relatively infrequent, compared with their occurrence in children living at home with their parents near at hand.

The frequency of enuresis has been so freely commented on, and the problem so thoroughly ventilated, that perhaps no more need be said of it. Interesting figures from the Huntingdon group give 26 out of 72 children in October and only 5 out of 22 in January, from 36% to 23%. Over the whole period 43 cases occurred in 127 children, but of these, only 18 were looked on as uncomplicated enuresis, without other neurotic difficulties.

What is true of enuresis is more dramatically so in the case of fæcal incontinence. The child psychiatrist has long since ceased to regard fæcal incontinence as a symptom of great rarity, or indicating a severe regression, since it is met with sporadically in a large number of emotionally disturbed children. This has been quite clearly brought out by evacuation, where a number of children, many of them over 5, and normally trained in clean habits, have shown this symptom. It seems likely that all cases are not due to an identical mechanism. In ordinary peace-time practice a high proportion of these cases occur in step- and foster-children, suggesting an uncertainty in their emotional relationships. In other cases the aggressive elements seem to predominate, the child using this as a final and desperate demonstration of anger or despair. Such mechanisms are largely unconscious, and it is doubtful if there are many instances in which the child is deliberately too careless to bother with the lavatory.

Naturally, educational problems tend to fall into the background with the modified school curriculum, and in any case they would be more a problem to the child and to the teacher than to the foster-parent, who would be taking the initiative in calling attention to the difficulty. And for those foster-parents who do raise difficulties, what, if any, scheme is going to be practicable in meeting their needs?

It seems clear that justice will not be done either to the children or to the foster-parents, unless the psychological aspect of the problems is taken into account. Can the smoothing out of such difficulties as do occur be left to the teachers who know the children so well, and to the billeting officers? Experience would suggest that while by these means difficulties will be being dealt with all the time, there will still remain a number of cases which will need a more detailed study. Even with all the facilities available at a fully staffed psychiatric clinic for children, it is no easy matter to distinguish the fundamental neurotic maladjustment from what is often a simple matter of training. Psychiatry should have a service to offer, both in distinguishing the mild from the severe problem, and in supervising the placing and subsequent care of children who show the more lasting type of difficulty. A psychiatrist might even find time to treat such cases, and so prevent their return to homes which will have played their part in creating the problem. By early diagnosis, they may forestall unsuitable placing, and may detect the few cases which are unlikely ever to make a successful adaptation. While a psychiatrist so employed would in no sense replace the workers who are already hard at such problems, he might well be able to direct their most useful efforts and spare them unnecessary ones. Can the existing facilities be regarded as adequate. Since child guidance clinics tend to be situated in towns,

and evacuation is mainly to the country, clearly there will be many children and many centres quite out of reach. This difficulty will be to some extent met by the provision, as suggested, of homes or hostels for the more difficult children. These will succeed or fail more by reason of the staff chosen to run them than by any details in equipment. Nevertheless equipment will be needed and expenses incurred. Can these homes be run by specially chosen foster-parents, and teachers, or will they be run by nurses, or by psychologists, and will they be consultation centres where a child psychiatrist can see selected cases ?

Without any elaborate machinery, how far is it going to be possible to give a medical officer in a reception area access to material, which may be very illuminating, on a known " problem child ", who has been evacuated. Is it better that such children should go with a dossier, to prevent mistakes, or with a clean sheet to prevent recriminations ? These and endless other questions suggest themselves for discussion.

It is an important step in community service that in the last few years an increasing number of local authorities have set up centres to treat the psychiatric problems of childhood. The child's close relation with his parents and with his school life has brought both home and school into the ambit, and too often the child psychiatrist has been feared as someone who might from his (or her) lofty position dictate to those, if not of riper years, at least of richer experience in the field of home management and education. No service can expect to live, except by the demand for it, but as we look into an uncertain future, it would seem as if the capacity to adjust readily to change would be at a higher premium than ever before. And so far as the civil population is concerned the brunt of the need to change has fallen on the children. Should there be a field here for child psychiatry, then it too must be prepared to adjust and adapt to changed conditions and, without lamenting unduly on past work which the war has undone, seek to provide a service for present needs. If the children have scattered, it should not be beyond the bounds of possibility to provide consultation centres and mobile psychiatrists who would serve a district. Such a service would only be effective if it were linked with the other medical services, and with the social and educational background in which the children are building up their new life.

Reference. — BOWLBY, RICKMANN, and WINNICOTT (1939), *Brit. M. J.*, Dec. 16 (in correspondence).

Dr. J. Ferguson : In interpreting the following facts it must be borne in mind that they relate to a Home County, viz. Surrey, on the very outskirts of, and with easy access to London, with highly developed education, medical, and hospital services of its own. Surrey is territorially a small county of about 700 square miles, densely populated (1,200,000) and no part of it is much more than 40 miles from London. Parts of it are themselves evacuation areas, parts are neutral areas, and the larger part of it is a series of reception areas. In the main it is a residential county, with a high rateable value per head of population. In all these respects Surrey is not quite typical of the average reception area, with its greater distances and its more sparse population.

Into this area last September we received some 35,000 evacuees from London, consisting of 23,812 school children, 11,000 children under school age, a number of whom were accompanied by their mothers. The population of the reception areas is about 322,000, so that in a period of three days we received an accretion of about 9%, which is about equal to the normal increase of six years in these areas.

According to the latest figures available our evacuees now number about 14,800 school children and 5,000 children under school age and mothers. So that the number of evacuated school children has fallen to 62% and of evacuated pre-school children to 45% of their original number.

The number of private families in our reception areas was at the time of the 1931 census 59,709, of separate dwellings was 56,408, and of separate rooms was 314,383.

These figures give some general idea of the billeting and the environmental public health problems. But when the children have been lodged they have to be educated or trained and their health has to be maintained. The normal school population of the reception areas is 25,888, so that we have had a percentage increase of 92%, and, broadly speaking, there was no excess of school accommodation for the normal school population. Again the normal child welfare arrangements were for a child population of 23,935, which has been increased by 46%. In the reception areas, therefore, our various services, educational and medical, had to deal with a population that had increased for some purposes by nearly 50% and for other purposes by nearly 100%.

Arrangements for Medical Examination of Evacuees on Arrival

The number of local authorities in Surrey which received evacuated persons from London was 13 (out of 33 in the county). Most elaborate arrangements were made for the actual transport of the evacuees and the evacuees were discharged from the trains at a large number of railheads, from which they were dispersed to their billets by buses. From the transport point of view a time-table, rigidly adhered to, was the heart of the problem, and this time-table constituted one of the main difficulties of the medical departments at this stage of the evacuation process. In every area, as far as the necessity for quick disposal necessitated by the transport arrangements, allowed, we were able to arrange for teams of doctors and nurses to examine the evacuees for conditions which could be detected in such a quick examination, e.g. general condition, presence of vermin, signs of infectious or contagious disease, crippling, and the like. In some districts sick bays had been prepared in advance to receive children whom it was deemed inadvisable to billet immediately.

My chief criticisms are :—

(1) Transport was allowed to dominate the process, so that parties in many cases did not arrive at the destination arranged for by the reception authority. (I must in fairness make it clear that transport is, in any case, a very complicated and delicate process, and it is probably quite inevitable that transport must influence powerfully any scheme of evacuation. From the technical point of view the transport arrangements worked with really wonderful smoothness.)

(2) While we must admit the technical excellence of the transport arrangements it would be a very great advantage if more time were available at the railhead for the children to be properly inspected medically before they are dispersed to their billets.

(3) There was too little consultation beforehand between the sending and the receiving authorities, and little information about the children was communicated by the sending authorities ; generally speaking we had to discover for ourselves which children were verminous or diseased or afflicted in any way. It would facilitate greatly both the billeting and the medical arrangements if fuller information about the children was given in advance by the sending authority ; in this way a great many billeting misfits would be avoided.

Problems encountered.—These fall under three main heads : (*a*) billeting, (*b*) educational, and (*c*) medical.

(*a*) *Billeting problems* have for us doctors a considerable importance and interest. Unsuitable billets may affect either the physical or the mental and moral health of the child, and a difficult child may make a comfortable household miserable. While it is true that better-class householders looked after their imposed guests in a satisfactory way and in many cases in a very exemplary and generous way, yet on the whole the most satisfactory billets were in decent working class homes in the country and in villages ; these foster-parents understood better the type of child who was billeted on them and their accustomed manner of life. The physical comforts may have been greater in the larger houses, but frequently the children are left to the care

of servants who resent their presence. A considerable number of difficulties were overcome and misfits successfully dealt with by experienced social workers, especially by our health visitors, who worked in close co-operation with the billeting officers—an arrangement which can be highly commended.

As regards the billeting aspect of evacuation I may summarize our experience in a series of statements :—

(1) The scheme cannot be considered a failure in spite of many difficulties or defects ; it has been more successful for school children than for younger children under school age. About 60% of the evacuated school children still remain, while only 45% of pre-school children remain.

(2) The scheme is not popular in the reception areas for obvious reasons : normal family life is too much disturbed even when the guests behave reasonably well. Nevertheless I must state definitely that there is less unwillingness on the part of householders to care for these evacuated children than is generally assumed without much evidence by those who have no first-hand acquaintance with the working of the scheme. Moreover, the children who remain are for the most part happy.

(3) School children of elementary school age are the most successful group, provided they come from reasonably good homes. Girls are more popular than boys with the foster parents.

(4) Children who have any abnormality either of behaviour or of health are unwelcome, and for these children hostels or sick bays should be provided. The difficult child can be dealt with in hostels or in some cases by re-billeting, but this class has tended to return home because they are often members of families with a small sense of social responsibility and are, therefore, not well disciplined.

(5) Older boys and girls are apt to be a problem ; often they are beyond the control of the ordinary householder and often they require more privacy and quiet if they are studying for examinations.

(6) Householders are generally unwilling to accept the work, worry, and responsibility of young children.

(7) As regards adults the scheme is a failure : adults either do not or will not fit in with the ordinary routine of their hosts ; too many of these adults have no sense of responsibility or desire to be helpful. They have mostly returned home.

(8) Mothers and children can be successfully dealt with only when their hosts can provide *separate* cooking, washing, and sanitary accommodation, or where they are billeted in cottages, flats, or other premises where they are self-contained and have to fend for themselves.

(9) The real " problem " child was comparatively rare, and we were able to deal with all that came to our notice by sending them to child guidance clinics.

(10) In spite of very many exceptions we think that on the whole there has been an improvement in the manners and self-discipline of the evacuated children. As I said earlier, the less satisfactory children have returned to London to their already unsatisfactory homes, which are the real cause of the trouble.

(*b*) *Educational problems.*—I do not suppose that anybody realizes more than the pædiatrician the close association of education and health and the importance of education in the improvement of the health both of the community and of the individual. But I will say no more here than that the educational facilities in the Surrey reception areas were before the war for some 26,000 elementary school children, whereas we received an extra 24,000 school children, of whom some 14,800 remain.

(*c*) *Medical problems.*—Great prominence has been given to some of these in the Press, notably to the prevalence of verminous conditions, enuresis, and behaviour problems, a prevalence considerably exaggerated. In an analysis of 6,800 evacuees a medical officer of health found that in his preliminary inspection at the railhead only 371, or 5·4%, were found to have defects detectable on rapid survey ; they

included 97 who were verminous, 3 with scabies, and 21 with impetigo. Perhaps these figures are not quite representative, the number of verminous children varying according to the type of evacuation district. From a very poor East End district 280 out of 2,583 were verminous (over 10%), whereas in the adjacent district verminous children were comparatively rare. In Surrey we regard a child as verminous which has even a single nit in his hair, and on this high standard last year 3·5% of our children were verminous. Excluding evacuees from the real East End about 5% of the children were verminous, but the degree of infestation was much worse than in our own children.

We dealt with the problem by drafting more health visitors into the reception areas, by extra sessions in our clinics, and by establishing special cleansing centres. Our principal trouble now is from reinfestation, the chief source of which is the visit from relatives from the evacuating area ; we inspect specially carefully on Mondays after the week-end visit.

Scabies and impetigo.—We have normally about 150 to 180 cases of scabies a year in our own 94,000 school children, and about 500 cases of impetigo. I have not yet seen actual figures, but my medical and nursing staff are definitely of the opinion that while there is more of both conditions than we are accustomed to, there is not any large or alarming amount. We have dealt with these conditions by admitting many cases into our own hospitals.

Enuresis.—This is probably far more common in children than we suspect, but a bed-wetter in his own home is a different problem from a bed-wetter in a strange (and often unwelcoming) household. Enuresis was not confined to those from bad homes. In large numbers the apparent cause of the condition was laziness or bad training, in others a desire to attract attention or interest, and in some pure naughtiness or perversity. Careful training is overcoming the defect, but our problem has been much eased by the return to London of the worst cases of the slothful or untrained type. We have even admitted some cases to hospital.

Ordinary illness.—Although far more children are being nursed by their foster parents, whether the illness be ordinary or infectious, than we had expected, foster parents, in general, do not like to have the responsibility of looking after other people's children when they are ill. The problem of illness has been dealt with in the following ways :—

(1) We have freely admitted sick children to our own hospitals, which contain at the present time about 7,000 beds for all classes of non-infectious disease.

(2) We have established some five sick bays for minor illnesses as well as eight hostels for unbilletable cases, including bed-wetters.

(3) Domiciliary medical and nursing services have been provided, the former through the local general practitioners at a capitation fee of 10s. a year, paid by the Government, and the latter through the local district nursing association at the immediate expense of the County Council.

(4) All the facilities of the school medical and the child welfare services have been made available and increased. We treat evacuated children exactly like our own children.

Infectious disease.—We have had no significant increase in the amount of infectious disease, either amongst our own children or amongst the evacuated children. Our fear that the evacuated children would infect our own children with strains of disease to which the latter were not immune, has so far happily not come true. Apart from any unexpected incidence of infectious disease, we have adequate isolation hospital accommodation for the infections usually treated in isolation hospital, but four small hospitals have been improvised, in addition, for the minor infections which do not usually enter an isolation hospital but which householders insist on having removed, especially if they have children of their own.

Has the Evacuation Scheme been Successful ?

In so far as evacuation was intended to remove children from danger to safety, the answer is " No ". An inadequate percentage of the population took advantage of the scheme in the first place, and of those who did very many returned—in Surrey 38% of school children and 54% of pre-school children and mothers. From the point of view of the householders the position as it is at present may be regarded as just tolerable, but certainly not welcome. The present hosts are on the whole doing their duty by their guests very well, and indeed very unselfishly. On all sides there is expert testimony to the marked improvement in the health and appearance of the evacuated children, and in the main to their improved conduct and discipline, the exceptions to the latter being the older children and adolescents. From the point of view of the receiving authorities their arrangements for dealing with the children in either physical or psychological departures from normal are fairly complete. In Surrey we have some 33 hostels, sick bays, or nurseries, established for the benefit of these children.

Suggestions for Future Evacuation.

(1) There must be co-operation and consultation *beforehand* between qualified and responsible officers of the sending and the receiving authorities.

(2) These experienced officers, who as teachers or as doctors are accustomed to deal with children, will assist the billeting officers of the local authorities in deciding to which billets particular children shall be sent.

(3) Visiting by parents is a difficult subject, and the point of view both of the parent and of the child must be considered ; from the point of view, however, of the reception authority, they too often unsettle the child or upset the foster parents or they reinfect children who have been cleansed.

(4) School parties should be kept as far as possible together and with their own teachers. As a class, the teachers have been simply splendid in the present evacuation.

(5) In so far as willing hosts can be obtained, domiciliary billeting is the best method for the ordinary elementary school child, but for the child under school age, or for the child who is "difficult" in any way, hostels or camps are the solution, but one must admit the great capital cost of camps. Secondary school children are best dealt with in camps or large houses on the lines of residential schools.

(6) Communal kitchens in villages are a great relief to foster parents and might be developed.

(7) Adults and large families should be lodged in large houses and given their own quarters.

Dr. Ethel Dukes said she had experience of three types of clinics in various parts of the county, viz. (1) Two clinics in residential homes for difficult children ; (2) a clinic in an evacuated L.C.C. school ; (3) a clinic in a hall under the auspices of the Women's Voluntary Services for Civil Defence, at which both elementary and secondary school children attended for treatment.

In the last named it had been possible to give talks to billeting officers and to foster-parents. The co-operation of most of the latter had been obtained in dealing with the problems in the home. They attended regularly with the children. It was in this clinic, too, that the best results had been obtained, and not in the residential homes as might have been expected. The question of obtaining the right kind of staff for these homes was a difficult one.

Dr. Dukes found that the greatest concern was aroused against problems of a sexual nature. Anything connected with sex produced horror amongst foster-parents, together with a fear of contamination in their own children. One boy,

who was punished for such misbehaviour in the privacy of his bedroom, betook himself to the open fields to continue his bad habits. The fact that this happened immediately after Sunday School made him the talk of the countryside. Next in order of annoyance came enuresis and soiling. Then destructiveness and unmanageableness. Only very few children had been brought on account of nervous or fearful symptoms where these existed alone and were not connected with enuresis, soiling, or misbehaviour. Nor had a single child been brought on account of educational backwardness alone. Foster-parents appeared to be anxious only about those manifestations that caused them annoyance and inconvenience or extra work.

Change of environment had helped in the elucidation of many problems existing before evacuation or developing as a result of it.

The question as to whether the foster-home was higher or lower in the social scale than the child's own home did not matter as much as it would to an adult. Children had different criteria and could adjust quite satisfactorily in homes that would not satisfy adults. All had been questioned, including many children who apparently had no problems. What they all appreciated most were the following: Love; understanding; kindness; lots of fun and jollity; being appreciated and given a feeling of importance, often by being allowed to help in the home, or by sharing alike with the foster parents' own children in work and play. They liked it very much if the foster-father took an interest in them and played or made things with them in the evenings. They liked being taken to "the pictures". They did not mind strictness. They liked good meals and the country. Very few said they wished to go back to London.

Dr. John Bowlby: Our experiences in Cambridge have been similar to Dr. Ferguson's in Surrey. Adolescent children have been a difficulty, especially those who want to return to London to get work. On the other hand, a surprisingly large proportion of children have settled down fairly happily. Of the 300 Tottenham children in Cambridge on December 1, only 25 were giving trouble or were obviously unhappy. Dr. Creak has remarked on the great difficulty of getting good foster-homes in time of peace. This has been my own experience, but in an emergency there are a remarkable number of people who are able and willing to give a good home to a strange child.

Arrangements for a future evacuation could be improved in several ways. For instance, there are certain children of difficult or delinquent character whom it is most unfair to billet in ordinary homes. Chronic thieves, children who have soiled themselves or wet their bed persistently in the past, and others of equally objectionable habits, should not be billeted in private houses but in hostels. Such hostels, however, must be properly staffed by people who understand difficult children and who can create a homely atmosphere. Elderly matrons of the type Dr. Dukes mentions are most unsuitable.

On the vexed question of camps, sending children to a camp for an indefinite period is very different from sending them to a preparatory school for fixed terms. For secondary school children, however, camps may be a satisfactory solution.

I cannot agree with Dr. Ferguson that small children under 5 should be put in communal hostels. For them individual care is of prime importance, and if this cannot be obtained in a good foster-home they are probably better left with their mothers. This is a problem to which my attention was directed before the war when I was engaged upon an investigation of chronic delinquency in children. Of 44 thieves seen at the London Child Guidance Clinic, 31 were persistent offenders. Of these 31 no less than 17 had histories of being moved during their first four or five years of life from one mother-figure to another. Sometimes they were in hospital for long periods, sometimes their mother died, and they were looked after by a succession of foster-mothers. But whatever the reason, none of them had had a stable relation

with one or two women as most small children do. Of a control group of 44 clinic cases who did not steal, only three had had a similar history. Despite the small numbers, this difference is statistically significant.

Dr. Winnicott said the distinction which Dr. Cameron had drawn between the pædiatrists and school medical officers and welfare doctors was important. It was the doctor who was fully trained in clinical pædiatrics whose services were not being used, and many of the well-known pædiatrists were actually so placed that they were looking after adults. Most of the problems that have arisen have been psychological, but surely it is better to hand over the organization of psychological services to physicians with the double training than to have children's bodies and emotions treated as if they were in separate compartments. It is possibly even now not too late for the authorities to ask the consultant pædiatrists of the country to organize the whole medical care of evacuated children.

The other point he wished to make was to draw attention to the need which exists now more than ever for a scientific study of the psychology of children. It is so easy for the detailed work to be lost sight of in a wild rush to deal with a large number of cases. Certain people get good results with children, even with difficult children, but this is not good enough. The problems arising out of evacuation must stimulate those who have the training to continue their detailed researches. Much is unknown about the mental mechanisms underlying incontinence and delinquency and research must be along the lines of the analysis of single cases.

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[*February* 26, 1940]

The X-ray Examination of Enamel

By J. Thewlis

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The work described in the present paper is based, broadly speaking, on two facts. The first is that the calcified part of the enamel is crystalline, and the second is that it absorbs X-rays much more heavily than the other constituents. Because it is crystalline the calcified portion has the property of diffracting X-rays (i.e. of scattering an X-ray beam in certain directions only instead of in every direction [1]), and from the way in which it does this the composition and structure of enamel have been determined. Owing to the heavy absorption of this portion its distribution within the enamel has also been ascertained.

The Constitution of Enamel

It is a well-known fact that enamel consists largely of inorganic material. There is, however, a certain amount of organic matter present which probably does not exceed about 2% by weight (Bowes and Murray, 1935). The composition of the organic portion has not been studied as yet by X-rays, and the present discussion is therefore restricted to a consideration of the inorganic material present.

If a fine beam of monochromatic X-rays (i.e. X-rays consisting of one wavelength only) is allowed to fall on a powdered crystal, and the diffracted beams are recorded on a photographic plate placed at right angles to the beam, as in fig. 1, a

[1] The term " crystalline " implies simply an orderly arrangement of atoms within a substance. This orderly arrangement is responsible for X-ray diffraction. Most solid bodies are crystalline, and a list of such bodies would include metals, wood, clays, refractories, and many other materials. Of the well-known types of solid body, glass is almost the only one which is not ordinarily crystalline.

pattern will be obtained which consists of a series of concentric circles of various intensities. This pattern is characteristic of the crystal under examination, being different for each substance, and is obtained whether the crystalline particles be macroscopic, microscopic, or submicroscopic. X-ray examination provides, therefore, a very useful means of identification, and when applied to enamel shows beyond doubt that the inorganic portion consists largely of some form of apatite, $Ca_{10}(PO_4)_6X_2$. In this formula X may be F, Cl or (OH), and chemical evidence suggests that in the case of enamel it is (OH), and that the apatite is therefore hydroxy-apatite (Bowes and Murray, 1935). The first X-ray diffraction photographs of enamel published by the author and by other workers were not sufficiently detailed to permit of a distinction being drawn between the various types of apatite, but from more recent photographs (Thewlis *et al.*, 1939) it can be seen that enamel does in fact consist largely of hydroxy-apatite.

Fig. 2, in which the most recent photographs are reproduced, shows that the X-ray diffraction patterns of dental enamel and hydroxy-apatite are remarkably

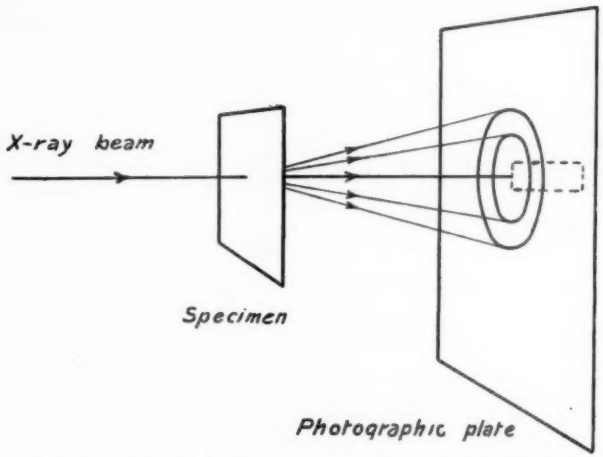

FIG. 1.—The diffraction of X-rays by a crystalline material.

similar, whereas those of fluor- and chlor-apatite are clearly different both from each other and from the rest. These photographs represent sections of a pattern such as that illustrated in fig. 1, corresponding to the portion outlined by dotted lines in that diagram, with the difference that a strip of film was used instead of a flat plate. The film was bent into the form of a cylinder of which the axis passed through the specimen.

Every crystal, be it large or small, is built up by the repetition of a certain grouping of atoms, characteristic of that crystal. This unit group of atoms, or "unit cell" as it is often called, is repeated over and over again in three dimensions in the same way as the pattern of a wall-paper is repeated in two, the nature and arrangement of the atoms in the unit determining the details of the X-ray diffraction.

The shape of the unit cell of apatite is that of a hexagonal prism and may be represented as in fig. 3, a crystal being made up by the continued repetition, in all directions, of the shaded portion in this diagram. The dimensions of the unit cell, which may be determined from the photographs reproduced in fig. 2, vary for the different types of apatite. They are given for apatites and enamels of various kinds

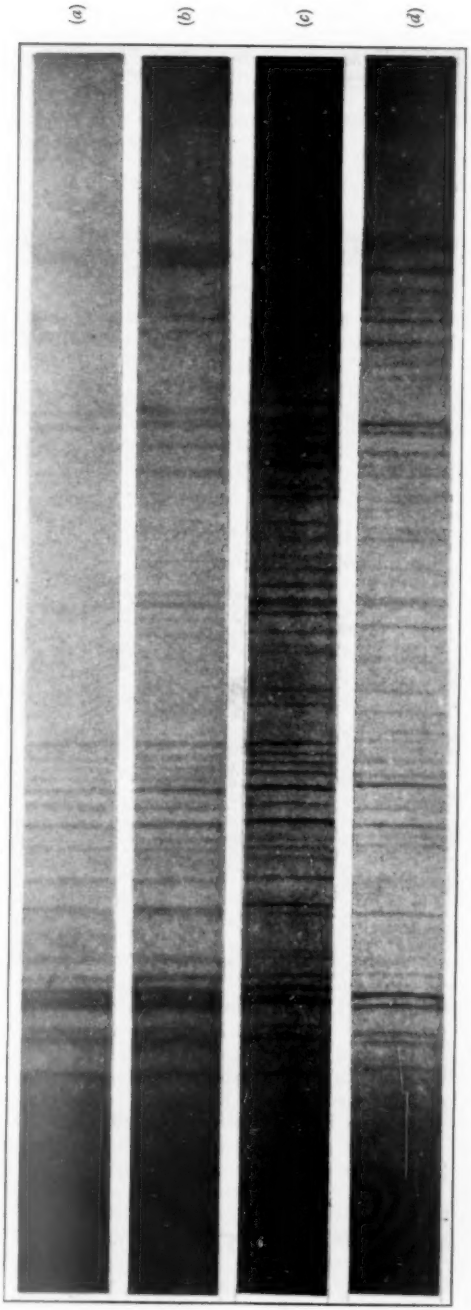

FIG. 2.—X-ray diffraction photographs of : (*a*) Human enamel ; (*b*) hydroxy-apatite ; (*c*) fluor-apatite ; (*d*) chlor-apatite.

in Table I. In this table the length of a side of the unit is denoted by "a" and the height by "c". These lengths are expressed, as is customary, in Angstroms ($1A = 10^{-8}$ cm.), and it will be seen that the similarity between enamel and hydroxy-apatite is again clearly demonstrated.

TABLE I.—UNIT CELL DIMENSIONS.

Material	a	c	c/a
Chlor-apatite..	9·57 A.	6·74 A.	0·704
Human enamel	9·41	6·87	0·730
Dogs' enamel	9·41	6·87	0·730
Hydroxy-apatite	9·41	6·87	0·730
Fluor-apatite	9·36	6·87	0·734

Chemical analysis (Bowes and Murray, 1935) shows that small amounts of magnesium and carbon dioxide are present in enamel, and it has been concluded (Thewlis *et al.*, 1939) that the former replaces some of the hydroxy-apatite calcium and that the latter probably exists as carbonate.

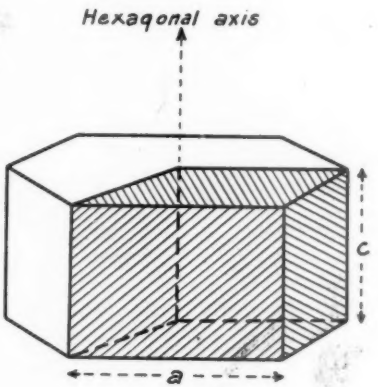

FIG. 3.—Hexagonal unit cell.

THE STRUCTURE OF ENAMEL

From measurements of the width of the lines of an X-ray diffraction pattern it is possible to calculate the average size of the crystalline particles which give rise to the pattern. When this is done for human enamel (Bale *et al.*, 1934) it is found that the average crystal size is about 0·3 μ. Now an enamel prism is at least as long as the enamel is thick, and its breadth is usually between 2 and 5 μ; hence it must contain a multitude of apatite crystallites (i.e. minute crystals). The question of the arrangement of these crystallites with respect to the prism at once arises.

It has already been stated that a powdered crystal gives rise to a diffraction pattern consisting of concentric circles of various intensities. In a powdered crystal the individual crystallites are of course arranged at random; if, however, a material is examined in which the crystallites are not arranged at random, but in some orderly fashion, the intensities of the concentric circles are found to vary not only from circle to circle but also in different parts of the same circle; and if the arrangement

is very well developed the pattern will consist not of complete circles but of short symmetrically situated arcs.

This is the type of photograph given by a section of enamel, from which it may be concluded that the apatite crystallites are here arranged according to some definite scheme. Such a photograph is reproduced in fig. 4. It was obtained by passing a fine beam of X-rays through a longitudinal tooth section of thickness about 0·1–0·2 mm., the photographic plate being set up as in fig. 1.

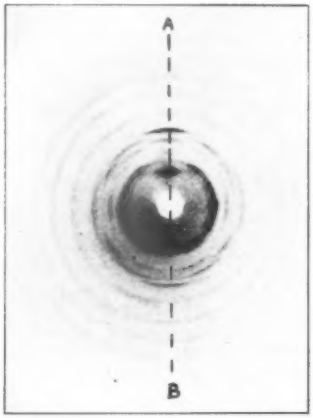

FIG. 4.—X-ray diffraction photograph of enamel section showing single fibre-axis AB.

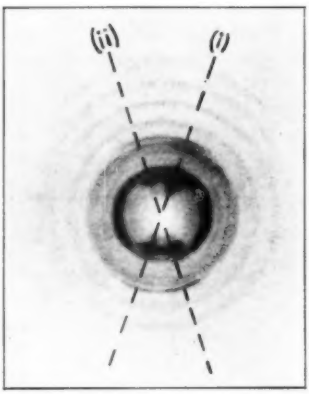

FIG. 5.—X-ray diffraction photograph of enamel section showing two fibre-axes (i) and (ii).

It has been shown (Thewlis, 1932, 1935) from photographs such as fig. 4, that the apatite crystallites are so arranged that their hexagonal axes (*see* fig. 3) tend to be parallel to the direction AB; and Table II shows how closely the observed results agree with those calculated on this basis.

TABLE II.—OBSERVED AND CALCULATED X-RAY RESULTS.

No. of ring	Crystallographic indices of reflecting plane	Angle between line AB and radius passing through mid-point of arc	
		Observed	Calculated
1	002	0°	0°
2	120·210	90	90
3	121·211	65	65·7
4	112	36	35·4
5	300	90	90
6	130·310	90	90
7	222	56	54·9
8	123·213	33	34·6
9	140·410	90	90
10	004	0	0

In this table the first column gives the number of the ring on which each arc lies, the innermost ring being number 1. The second column gives the crystallographic

indices [1] of the corresponding planes. The third column gives the observed angles between a line such as AB in fig. 4 and radii passing through the mid-points of the various arcs; and the fourth gives the calculated values of these angles.

A direction in a body to which the crystal axes tend to be parallel is known technically as a "fibre-axis." In dogs' enamel there is, at each point, one such axis, but in human enamel (both deciduous and permanent) two fibre-axes are often noted, and the arcs of fig. 4 are then doubled as in fig. 5. In this photograph the fibre-axis directions are indicated by the lines (i) and (ii).

The two fibre-axis directions in human enamel, to which the hexagonal axes of the hydroxy-apatite crystallites tend to be parallel, may be seen from fig. 5 to be inclined to each other at an angle of about 30°. The two sets of arcs in this photograph are roughly of the same intensity, but it is usually found that one set is stronger than the other, the majority of the crystallites having their axes parallel to the corresponding fibre-axis.

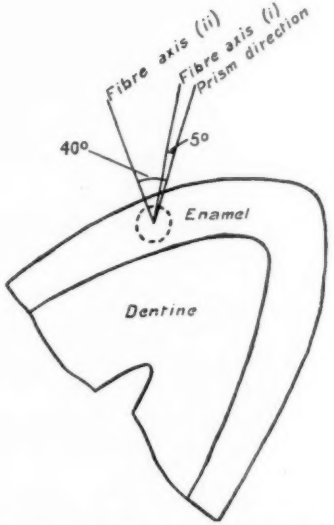

FIG. 6.—Diagram of a tooth section showing the relationship of the prism and fibre-axis directions to each other and to the tooth.

The arrangement of the crystallites with respect to the prisms has been determined for human deciduous enamel by comparing the X-ray photographs of a number of enamel "areas" with their photomicrographs (Thewlis, 1939*a*). This work has shown that the direction to which a majority of the crystallite axes tend to be parallel (fibre-axis (i)) makes an angle of about 5° with the prism direction, whereas the other fibre-axis (fibre-axis (ii)) is inclined to it at about 40°. The fibre-axes point to that side of the prism remote from the tip of the nearest cusp, the directions being taken away from the tooth. A diagrammatic illustration of this result is given in fig. 6.

In the course of the investigation it was established that both groups of crystallites (i.e. those with their axes inclined at 5° and 40° respectively) are present in individual

[1] These are the Miller indices which specify geometrically any plane in a crystal. The interested reader may acquaint himself with their use by consulting any work on crystallography or X-ray analysis.

prisms, within which variations in the degree of perfection of the crystalline arrangement may occur. These variations give rise to different types of X-ray photograph, which are referred to later.

The investigation also showed that one or both of the two groups of crystallites present in the prism material may also be present in the interprismatic substance. X-ray examination alone gives no further information, but when the X-ray results are combined with the results of examination by the polarizing microscope a picture of the structure of the interprismatic substance may be obtained. This involves a calculation of the optical properties of enamel (Thewlis, 1939*b*), which is outside the scope of the present paper; and the conclusion arrived at is that whereas the prism material is characterized in general by a predominance of the 5° group of

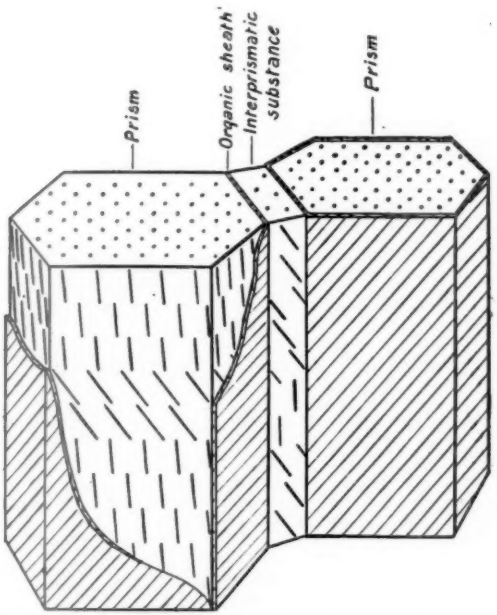

FIG. 7.—Diagram illustrating the submicroscopic structure of enamel. The directions of the crystallite axes are represented by short lines.

crystallites, the 40° group usually predominates in the interprismatic substance. A given portion of enamel, however, rarely contains as many 40° as 5° crystallites, and indeed the 40° group is sometimes entirely absent. This conception explains the optical properties exhibited by the prisms and the interprismatic substance both in longitudinal and transverse sections of prisms.

The submicroscopic structure of enamel, according to the ideas outlined above, is illustrated diagrammatically in fig. 7. Two prisms with their organic sheaths and the interprismatic substance are drawn, the organic sheath having been cut away from one prism so as to reveal the arrangement of crystallites within. These crystallites are represented by short lines which signify the directions of the crystallite axes. They are arranged in rows in order the more easily to illustrate the relative

numbers belonging to the 5° and 40° groups. The actual positions of the crystallites as distinct from their directions are, of course, unknown.

Three different types of crystallite arrangement, varying in degree of perfection, have been recognized and are illustrated in fig. 8, together with the X-ray photographs to which they give rise. These photographs will be seen to differ in the intensity and sharpness of the diffraction arcs. Similar types of X-ray photograph are also found to occur as a result of differences in the degree of prism regularity.

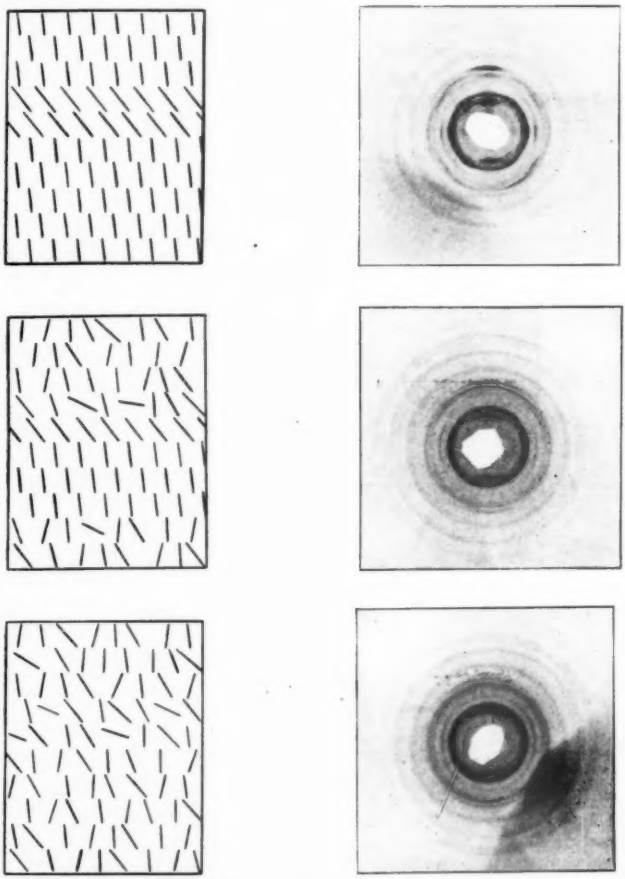

FIG. 8.—Different types of intra-prismatic crystallite arrangement, with corresponding X-ray diffraction photographs.

THE DEGREE OF CALCIFICATION OF ENAMEL

As already indicated, the calcified portion of a tooth absorbs X-rays to a much greater extent than the other constituents, and it is therefore possible to detect variations in the degree of calcification by radiographic examination.

If a tooth section is placed in contact with a photographic plate or film and exposed to a beam of X-rays the resulting radiograph will be most dense in those places that correspond to the lowest degree of calcification. Thus the dentine will give rise to a denser shadow than will the enamel, and local variations in the degree of calcification will give rise to corresponding variations in photographic density.

In this way it has been found that Schreger's bands (Hollander *et al.*, 1933, 1935), the striæ of Retzius, incipient caries and enamel spindles (Hollander *et al.*, 1933; Applebaum *et al.*, 1933), and mottled enamel (Applebaum, 1936) are all associated with local variations in the degree of calcification. It has also been shown (Thewlis, 1937*a*) that areas of enamel which have taken up stain, and the discoloured areas sometimes referred to as " pigmented " (M. Mellanby, 1934), tend to possess a low degree of calcification.

The author's work has been concerned mainly with the determination of the general features of enamel calcification, and with the development of a radiographic method capable of use not only qualitatively but also quantitatively, the object being to determine the degree of calcification in terms of the actual percentage of calcific matter present.

For such work it is essential that an X-ray beam of known wave-length be employed, since the X-ray absorption, upon the measurement of which any quantitative method must depend, varies markedly with wave-length. Consequently the so-called " grenz " rays, which have been widely used for the radiographic examination of teeth, are not suitable. These rays consist of " white " radiation produced at a low voltage, and are composed of X-rays with a range of relatively long wave-lengths, the values and relative intensities of which are uncertain. The characteristic K radiation of copper, of which the wave-lengths are accurately known, has therefore been used for the radiographic work described in this paper.

Radiographic methods for the quantitative measurement of the X-ray absorption of teeth have been described by Hollander (1935, 1936), Hollander and Vesely (1936), and by Hodge *et al.* (1935), but in each case the authors have restricted themselves, in effect, to a determination of that thickness of a suitable metal which is equivalent in absorption (under specified conditions) to the part of the tooth examined. Although Hollander uses a very sensitive ionization method in his comparisons, which is claimed to be liable to an error of only $\pm 0{\cdot}3\%$, he employs white radiation (*see above*) consisting of a range of indeterminate wave-lengths; and the extension of his results to the absolute determination of absorption, and hence to the estimation of the actual percentage of calcific matter present, is therefore out of the question. A similar remark applies to the densitometric method of Hodge *et al.* Both methods suffer, too, from the disadvantage that only relatively large areas of the tooth section can be examined at one time, a circular disc of 1 mm. diameter being examined by Hollander's method and an area of similar size by that of Hodge *et al.* By a development of the microphotometer method previously used (Thewlis, 1937*a* and *b*) the degree of calcification may, however, be measured from point to point throughout any desired portion of a tooth, continuous changes may thus be followed, and " line " effects, which would perhaps be missed by other methods, can be detected and measured with comparative ease.

The instrument used is the Moll self-recording microphotometer, in which a very fine beam of light passes through the radiograph under examination and falls on a thermopile, the resulting current being measured by a galvanometer, the deflection of which is recorded by a spot of light on a moving drum of bromide paper. The drum is geared to the plate holder, which moves so as to draw the radiograph across the original beam of light, and since the thermopile current is a measure of the photographic density, there is obtained on the bromide paper a record of the variations in density across the portion of the radiograph examined, and hence a record of the variations in the degree of calcification across the corresponding portion of the tooth section.

Fig. 9 is a typical microphotometer record obtained by the examination of enamel. The zero line in this record corresponds to infinite photographic density, i.e. to total blackness, and therefore to a complete lack of calcification. The higher any part of such a record is above this line the greater is the X-ray absorption, and hence the degree of calcification, in the corresponding part of the tooth.

It will be seen from fig. 9 that at the outer edge of the enamel the record shows a peak, labelled A. This corresponds on the radiograph itself to a line bordering the outer edge of the enamel, which is less dense than the rest of the enamel and appears white by contrast.

This effect suggests that the X-ray absorption, and therefore the degree of calcification, is higher at the outer edge than in the rest of the enamel, and it was accordingly concluded (Thewlis, 1934) that an outer "hypercalcified" layer was present. It was pointed out, however, by Hollander and Saper (1935) that a photographic effect,

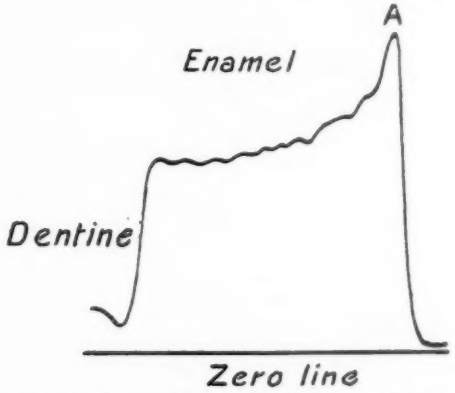

Fig. 9.—Microphotometer record taken across the enamel.

known as the "Mackie" effect, might account for the presence of the white line on the radiographs. They obtained a radiograph of aluminium sheet showing this effect along the edge, and the author has repeated their experiment with the same result. In spite of this there are certain facts that seem to indicate that the white line in radiographs of enamel might be due to true hypercalcification in addition to the Mackie effect. This line is found to persist through an incipient caries lesion (dark on the radiograph) when it has been almost completely eliminated from the remainder of the enamel adjacent to it. Since strong contrast is necessary for the presence of the photographic effect, whereas in this case areas of roughly equal density lie on each side of the white line, the latter can hardly be photographic in origin. Moreover, it is found that the white line sometimes varies in intensity and width in different parts of the same section, which suggests that an effect due to hypercalcification may be superimposed on the photographic effect. Radiographs showing the extensions of the white line into an incipient caries lesion have been published by Hollander and Saper (1935) and by Applebaum (1938).

In view of this uncertainty a series of experiments was made (Thewlis, 1937*b*) with the aid of the microphotometer in order to test the possibility of the white line being due in part to true hypercalcification. In these experiments microphotometer records taken across the radiograph of the outer enamel edge were compared with those taken across a nearby broken-off edge of enamel. A number of examples were

considered, and it was found that true hypercalcification did occur in many cases. In such cases the intensity of the microphotometric peak corresponding to the outer enamel edge was found to be three or four times greater than that corresponding to the broken-off edge.

The experiments also revealed the existence of a gradient of calcification in the enamel. This may be seen in fig. 9, in which it will be noticed that the height of the record above the zero line decreases as the distance from the enamel surface increases. Such a gradient was noted in the majority of the teeth examined and was shown not to be photographic in origin. It was therefore concluded that the degree of calcification decreased steadily from the enamel surface to the amelo-dentinal junction.[1] The hypercalcified layer referred to above may be considered as a culmination of this observed gradient of calcification.

The significance of the steady change in degree of calcification across the enamel is clearly of interest. The fact that the surface enamel is harder than the interior enamel, which has been reported by Karlström (1931) and by Hodge and McKay (1933) is now explained. The figures of the latter workers may be noted in this connexion. They find that " the hardness of the enamel varies from 330 to 910 as we go from the dentine through about nine-tenths of the thickness of the enamel, while the extreme outer edge, both of occlusal and buccal enamel, maintains a maximum value of 2,050 ".

The degree of calcification of enamel also affects its birefringence, and it has been shown (Thewlis, 1940) that the examination of enamel by the polarizing microscope gives results which are in agreement with the above X-ray results. The latter also confirm the finding of Karlström (1931) that the surface enamel possesses a higher specific gravity than does the interior enamel.

So far we have been concerned with qualitative measurements of a relative character, but as already indicated, a method has recently been developed (Thewlis, 1940) by which the degree of calcification may be expressed in terms of the actual amount of calcific matter present. This method involves the absolute determination of the X-ray absorption at a given point in the enamel; from which, since the absorption due to each constituent of enamel is known, the amount of calcific matter can be calculated. Applications of the method to a human tooth section, taken at random, showed that the amount of calcific material present in the enamel was about 92% by volume. This figure is not necessarily typical, and further work will have to be carried out before any general conclusions can be drawn or any average figures put forward.

The method can in no way be regarded as a substitute for chemical analysis. By its use, however, the amount of calcific material present in a given volume of enamel may be determined. This varies from place to place in the enamel, and may be different for different teeth, even though the calcific matter itself might give the same chemical analysis each time. (No chemical method would, of course, be capable of giving separate analyses for a continuous series of points in a tooth such as can be examined by the microphotometric method.)

The importance of this is obvious, for some aspects of the behaviour of a tooth may well be related to the amount rather than to the chemical composition of the inorganic material.

A complete discussion of the work as a whole has appeared in the Medical Research Council's Special Report Series (Thewlis, 1940).

ACKNOWLEDGMENTS

This work was carried out on behalf of the Medical Research Council's Committee on Dental Disease, and the author is indebted to them for permission to publish the results.

[1] A similar conclusion was arrived at independently by Hodge *et al.* (1937).

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Section of Epidemiology and State Medicine

President—J. A. GLOVER, O.B.E., M.D.

[*April* 5, 1940]

Evacuation: Some Epidemiological Observations on the First Four Months

PRESIDENT'S ADDRESS

By J. ALISON GLOVER, O.B.E., M.D., F.R.C.P., D.P.H.

Dr. Glover's historical introduction (I. The Past) has had to be omitted owing to paper shortage

II. THE PRESENT

(1) *Preparation*

The policy of evacuation with the threefold objective of (*a*) dispersal in view of the threatened aerial bombardment of London and other cities, (*b*) the preservation of the morale of the civil population with the corollary of enabling the country to develop its maximum war potential from the word "go", and (*c*) the preservation of the continued social care and education of the children and their insulation so far as possible from the psychological shocks which bombardment from the air might inflict, was first fully considered in all its bearings by the Anderson Committee. This Committee was appointed in May 1938, and reported [12] in July of that year. The Government endorsement of the policy and the publication of the report was, however, delayed by the "Munich" crisis, in the course of which plans had been hurriedly prepared for the removal of some 400,000 school children from London and large numbers from other areas such as Birmingham, while some 1,200 nursery school children and 3,500 physically defective children had actually been sent out of London.

Immediately after the Munich settlement the responsibility for the formulation of a scheme was placed upon the Ministry of Health and a strong Advisory Committee representative of the local authorities, the local education authorities, and the teachers was appointed. This Committee suggested that rather than attempt any general evacuation of all persons, whether children or adults, who were not indispensable, the official scheme should be confined to the evacuation of certain "priority" classes. These classes were school children who would go in school units with their teachers, children under 5 who would have to be accompanied by their mothers or some other responsible adult, expectant mothers, the adult blind and certain adult cripples where removal was feasible. The Anderson report had emphasized that the scheme must be on a basis of voluntary evacuation, and that billeting in privately occupied houses

must inevitably, on account of the great numbers involved, be the main method of housing those sent out ; compulsory powers of billeting would have to be taken, but voluntary arrangements should be relied upon as much as possible, especially in the case of school children.

So familiar are we all with the general outline of the preparations for this great undertaking that they may be summarized in a few lines. England and Wales (and Scotland, though this paper is only concerned with the first two) were divided into three types of area : *Evacuation Areas* 81 in number, selected after taking into account their size, their density, and their vulnerability—from these 81 areas the school children and the other priority classes were to be sent ; *Reception Areas*, of which there are 1,100—chiefly small towns or rural parts of the country where the priority classes were to be received ; and *Neutral Areas*, which would neither send out nor receive persons from other areas.

Some great centres, like London, were " wholly " evacuable ; others, like Manchester, were " zoned ", i.e. divided into evacuation and neutral areas.

On this geographical basis, the Ministries of Health and Transport, and the Board of Education, in consultation with the local authorities of the 81 evacuation and the 1,100 reception areas, the main-line railways, and the London Passenger Transport Board, prepared a scheme to meet the enormous difficulties of the task, which a substantial number of unofficial evacuees increased. Transport arrangements were planned to the last detail by the Transport authorities, and two days' rations for all official evacuees were stored in the reception areas.

The number of evacuable persons of the " priority " classes living in the evacuation areas was estimated at some 3,644,000, half of whom would be school children ; and of this total evacuable population it was expected that some 80% or say, 2,900,000 persons would avail themselves of the official machinery for evacuation.

The school children were to be evacuated by schools in charge of their teachers and other voluntary helpers, and to be accommodated in billets in the reception areas. The billeting standard adopted was one person to every bed- or living-room of a house. A certain number of special schools were to go to camps, and 150 nursery schools, as parties, to large private houses.

Every endeavour was made to obtain billets voluntarily, and the response from householders was such that offers to accommodate over 2,000,000 school children were received as against an " expected " number of 1,400,000 school children to be evacuated. The cost of feeding and billeting the children, and of their medical attendance, was to be met by the Government, though contributions towards the cost of these allowances was to be called for where the family circumstances justified such a course. The combined " London and outer-Metropolitan areas " formed the most difficult problem, as it occupied some 250 square miles and had some 813,000 school children.

The hospitals in the evacuation areas were also to be evacuated, patients able to go home to be sent there, patients fit to be moved but not to be discharged, to be transferred to country hospitals by ambulance, patients unfit to be moved, to remain.

(2) *Epidemiological Preparations*

The Ministry of Health, which was at the same time preparing on a gigantic scale the emergency medical service for air-raid casualties, arranged with the local authorities for increased *hospital provision for infectious diseases* in the reception areas.

To provide for the reception of expectant mothers " *Obstetric Areas* " were defined according to the accessibility of maternity hospitals. In these obstetric areas 137 emergency maternity homes, staffed by qualified maternity nurses and containing 3,700 additional beds, were provided for normal cases. Consultant obstetric services and hospital accommodation were provided for abnormal cases, and arrangements made for the prompt isolation of any case of puerperal pyrexia. *Hostels* were provided

for expectant mothers accompanied by young children where the children could be cared for during the mother's confinement.

The Ministry also arranged by agreement with the British Medical Association for the *domiciliary treatment of evacuated children*.

The Medical Research Council organized two central and 23 subsidiary *laboratories* to augment the facilities already existing in the evacuation areas. Water supplies, sewerage, and drainage, were also increased in many areas.

The Board of Education, in May 1939, in a section of its far-seeing Circular 1469, emphasized the risk of contagious and infectious diseases and the preventive measures in which (though primarily they were the duty of the Health Authority), the co-operation of the School Medical Service was essential. The *contagious diseases*—pediculosis, impetigo, and scabies—would be the main problems at first, and in-patient accommodation for their treatment might be required, as well as facilities for the out-patient treatment of children, baths, and the disinfection and disinfestation of clothes and bedding. Existing baths in schools and baths and steam disinfectors in public institutions should be mapped out in consultation with the local health authority, schemes of treatment drawn up, and additional personnel for working the steam disinfectors trained. The augmentation of the medical and nursing staffs, particularly for inspection for cleanliness and cleansing, was advised.

With regard to *infectious diseases*, the most imminent risks naturally seemed to be of the epidemic spread of those whose seasonal maxima occur in autumn, such as poliomyelitis, diphtheria, scarlet fever, enteric fever, and dysentery.

> The Board urged school medical officers who, in many reception areas, were also medical officers of health, to plan or assist in such sanitary precautions as the provision of emergency standpipes, ablution arrangements, latrines, and the disposal of sullage water in villages; to undertake the examination of contacts, both home and school; and to assist in any scheme of immunization which the local health authority already possessed or might organize for the occasion.

Unfortunately this excellent advice fell upon the ears of authorities and medical officers already overwhelmed by duties relating to air-raid precautions and the treatment of casualties, to which precedence had been given both officially and by the general expectation of an intensive period of air bombardment at the outset of war. This expectation fortunately proved erroneous. Those who criticize subsequent events seem to forget that all preparations were based on this expectation, which was almost universally held.

(3) *Exodus*

On Thursday, August 31, evacuation was announced for the next day. On Friday, September 1, the main bulk of the school children with their teachers and helpers were moved, and on Saturday for the most part mothers and accompanied children. When war was declared on September 3 nearly all the children who availed themselves of the move were already in reception areas. Some 80,000 persons from the Metropolitan and outer-Metropolitan areas, including school children, expectant mothers in their later months, blind and deaf persons, and some special schools, travelled by motor bus. 23,000, mostly school children, were taken by steamboat from the Thames to Norfolk and Suffolk, and conveyed inland by motor bus after disembarkation at Lowestoft and Yarmouth. The rest travelled by train from many emergency railheads, to avoid congestion at termini. The whole movement, which was finished on Monday, worked like clockwork, and was a miracle of organization. Trains arrived on time, and there was scarcely a casualty. Ordinary traffic was somewhat interfered with, but a substantial skeleton service was run for ordinary travellers, who suffered little or no inconvenience. The English climate, kind for once, materially assisted, both in the exodus and in the settling-in process, by a spell of perfect weather. We English belittle our national achievements. Here was one which hardly any nation could have equalled, and certainly no other nation could

have carried through in so kindly, cheerful, and matter-of-fact a way. We should be proud to have such organizers

> " . . . who did their deed
> and scorned to blot it with a name "

while transport officials, guards, porters, bus drivers, and conductors, teachers, escorts, receiving and billeting officers, showed the utmost resource and kindness. The behaviour of the children during the long hot and tiring day was exemplary.

Billeting, on the whole, was successful, particularly as regards unaccompanied children who were sorted out, despatched to the receiving towns and villages, and thence distributed to their billets, generally with a minimum of delay.

In addition to the billeting of normal children, the evacuation of two other small but important groups of children must be mentioned.

Thirty camps (22 of them privately owned holiday camps, eight of them National Council or Social Service or Y.M.C.A. camps) were occupied on evacuation (with one exception) by *handicapped children* (deaf, cripples, heart cases, and mental defectives) who could not reasonably be billeted, either in the interests of the children themselves or in those of householders. The total number of such children who left London, Birmingham, Newcastle, and Gateshead for these camps was 5,087. Further, and to raise even greater epidemiological problems, some 55 day and 36 residential nurseries normally containing about 2,400 and 1,500 children respectively, and 59 nursery schools, with a normal accommodation of about 3,500, were evacuated as units from evacuation areas in England, mostly to large country houses.

(4) *Numbers*

The plan, as I have said, estimated that the total evacuable population in the zoned portions of the evacuation areas was some 3,644,000, of whom half were school children. The decision was, however, left to parents, and found less than half willing to send their children. In the event only some 1,270,000 persons or 33% of the total evacuable population, went to the reception areas under the official scheme. The voluntary evacuation was also very large indeed. Of this total of 1,270,000 who went under the official scheme, 166,200 were mothers or other adults " accompanied " by 260,300 young children ; 12,291 were expectant mothers ; and 734,883 school children " unaccompanied " (i.e. by their mothers). The remainder, apart from some 5,000 blind or crippled persons, were teachers and helpers. The 734,883 school children are by far the most important from the epidemiological point of view for they were not only by far the most numerous section, but they were also the more permanent settlers (as will be seen by Diagram I) and owing to school were brought intimately into wider contacts with the " native " children.

But this shifting of three-quarters of a million school children from the great cities to the small towns and villages was but one of the epidemiological factors. Far larger numbers of school children were materially affected by evacuation, though they were not actually moved. The daily environment of the school population which stayed behind in, or drifted back to, the evacuation areas was profoundly changed by the universal school closure in these areas. In the neutral areas many schools were closed for many weeks, some were overcrowded, others worked on double shift. In the reception areas the native children were working half-time in consequence of the double shift, and in addition their bacteriological environment was altered by contact with the nasopharyngeal flora of their new school- and house-mates.

Thus, in round numbers, official evacuation (Diagram II) increased the school population of the reception areas by 735,000 from 1,958,000 to 2,693,000, and thus diminished that of the evacuation areas from 1,914,000 to 1,179,000. Unofficial evacuation increased the change, but by how much it is hard to say. The neutral

areas containing 1,070,000 school children are shown as if they had remained unchanged, though probably there was not a little unofficial evacuation even from them.

The "drift back", of which more hereafter, by mid-January had brought figures to 2,377,000 in the reception, and 1,495,000 in the evacuation areas.

Though these changes look small in a diagram the columns of which 1/20th" = 100,000 children, yet the change in some rural areas was great.

The impact of the great Metropolitan and Outer Metropolitan evacuation of 366,800 school children naturally was most felt in the Home Counties. Surrey is zoned into evacuation, neutral, and reception areas. In its reception areas, Dr. Ferguson [10] has told us, the school population received evacuee school children, equal

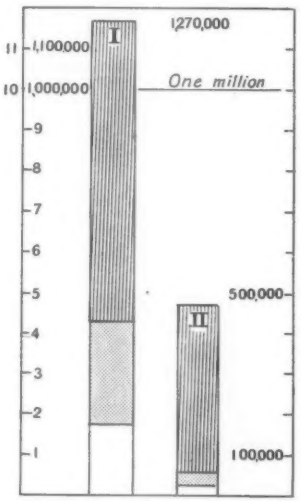

DIAGRAM I.—The "drift back". Column I. Evacuation. Column II. January 8, 1940. Shaded portion = school children. Dotted portion = accompanied young children. Blank portion = mothers.

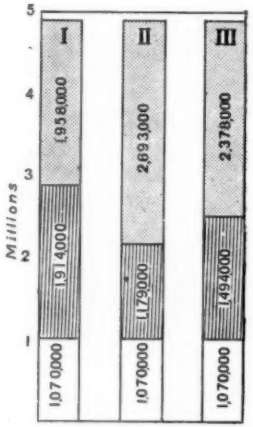

DIAGRAM II.—Showing approximate school population in evacuation areas (vertical shading), reception areas (dotted), and neutral areas (blank). I. Before evacuation. II. Immediately after. III. Four months after—the result of the "drift back".

in number to 93% of its "native" school children, as well as a number of younger children under 5 ("accompanied") equal to 43% of the estimated under 5 "native" children. Surrey in mid-January still retained 76% of its evacuee scholars, a very satisfactory proportion when its proximity to their homes is considered; Sussex (East) with the accommodation afforded by its great holiday towns naturally received a number (43,444) greater than any other receiving area, Kent being next with 38,054.

Owing to the difficulties of transport over long distances, some counties received comparatively small numbers of school children, Cornwall for example had 1,250. Military requirements, of course, diminished the numbers of billets which some reception areas could afford for civil evacuees.

The evacuation areas also varied much in the proportion of children sent. London

sent 48% of its estimated school population. Manchester rather more than 66%, Sheffield only about 10%; both are "zoned" areas, but this does not account for the striking difference.

Similar variations in the proportions of children sent occurred in groups or pairs of neighbouring areas where risks appeared identical.

The Drift Back

No sooner was evacuation completed than, in the absence of air attack, the drift back of mothers and accompanied children began. In six weeks nearly three-quarters had returned from some areas. The expectant mothers stayed longer and returned, when they did return, as a rule only after the completion of the puerperium; but at the end of the four and a quarter months only 1,052 of the 12,291 originally evacuated were still in the reception areas. At the end of four and a quarter months, of 166,200 mothers 145,700, or 87%, had returned to their evacuation area homes, and 223,400,

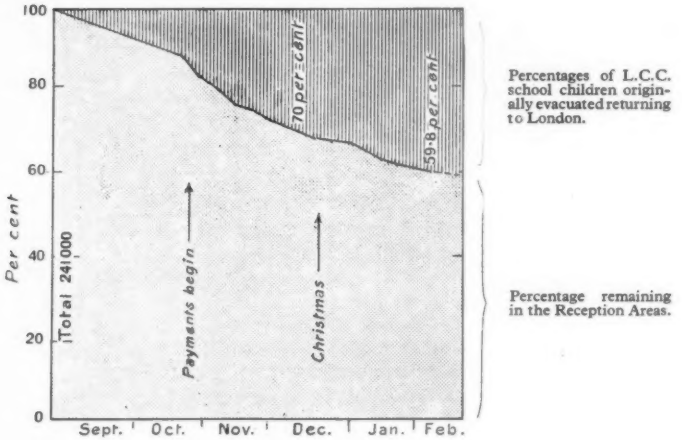

DIAGRAM III.—The "drift back" of London children.

or 86%, out of 260,300 accompanied children with them. I need not here do more than record these changes which are obviously of epidemiological importance. The causes are well known.

Diagram I shows the position of the categories at evacuation, and at the end of four and a quarter months, when only 20,500 mothers, 36,900 accompanied children, and 418,442 school children remained in the reception areas.

Of the total 1,161,363 mothers and children evacuated, 685,521, or 59%, had returned.

The drift back of the school children was, however, much less rapid, though it varied greatly in different districts, the main factors influencing it seeming to be (1) proximity to home, (2) parental opinion as to the comparative safety of the reception and evacuation area, (3) the amenities of the reception area.

Diagram III shows the drift back of London children. London evacuated some 48% of her school population, and has been as successful as most in keeping her evacuees in the reception areas. The rate of return, though not shown in detail

for the first seven weeks, shows an acceleration when payment was first required, then a slowing. The effect of Christmas is less obvious than might be expected, and the rate now seems stabilized.

III. Epidemiology

A. Infectious Diseases

When I recall my gloomy expectations in the anxious months before the war, expectations shared, as the medical journals[1] show, by many others, I realize how much we have to be thankful for. The infectious diseases with an autumnal prevalence constitute a formidable group, including diphtheria, scarlet fever, poliomyelitis, enteric fever, puerperal fever, rheumatic fever, and epidemic jaundice. The usual maximum for diarrhœa is in September, that of dysentery but a little earlier in the year.

Diphtheria and scarlet fever had shown high incidences in 1938 and recent previous years, and seemed likely to flare up still higher if town carriers and country susceptibles

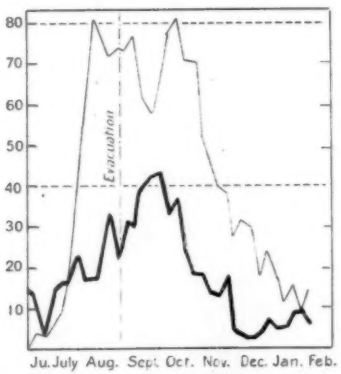

Diagram IV.—Acute poliomyelitis, weekly incidence.
Thin line—1938. Heavy line—1939.

were freely mixed. Poliomyelitis, the unwelcome visitor of 1938, had up to mid-July seemed to threaten as much as in that year.

Both dysentery and enteric had shown increases in the two months previous to war. Yet how providential was the outcome!

The incidence of infectious diseases in the first four war months was remarkably low. Notifications of diphtheria, scarlet fever, and poliomyelitis, were all much less than in the corresponding period of 1938. Nor was there subsequent to evacuation any real increase in enteric fever or dysentery. As regards many of the respiratory diseases spread by "droplet" infection which cause so much trouble in schools—such as measles, whooping-cough, influenza, and feverish cold, it was fortunate that evacuation took place in the beginning of September. This, as the Epidemic in Schools Inquiry (2b) showed so clearly is, as regards these diseases, one of the healthiest periods of the year.

Most of the reception education authorities had at first to adopt the "double

[1] Vide *Lancet*, 1939 (ii), 605; *Med. Officer*, 1939, **61**, 174, 192, 201, and many others.

shift " method of schooling. This enabled the children, both native and evacuee, to spend half their time in the open air with organized games and walks in the splendid autumn weather of the first two months. This acclimatized the evacuated town children, and allowed the native children to acquire some immunity, by small and gradual dosage, to any fresh infective strains their new home- and school-mates might bring with them.

I shall now speak of some of these diseases *seriatim*.

Poliomyelitis.—The dispersal of hundreds of thousands of city children in villages in autumn seemed just the setting of an outbreak, particularly as I have said, in mid-July cases were as numerous and widespread and showed the same tendency to centre on London and the Home Counties as in the epidemic of 1938.

Evacuation was followed by a small exacerbation which soon died away. Diagram IV shows the striking difference between the 370 cases in the four war months of 1939 and the 927 of the corresponding period of 1938.

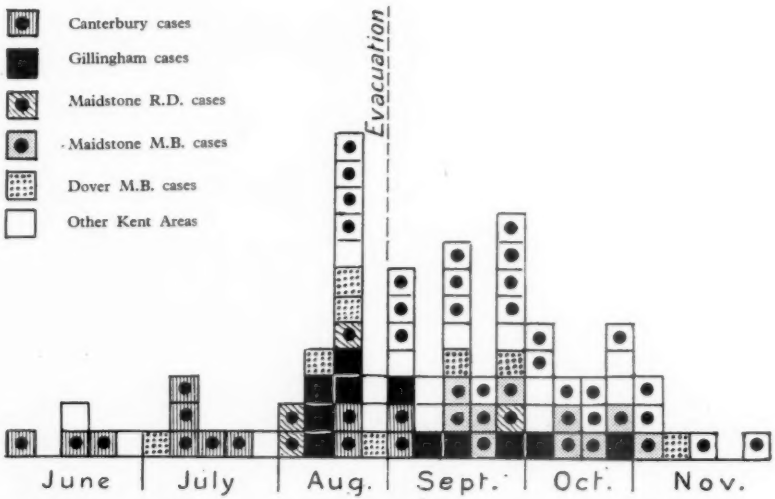

DIAGRAM V.—Incidence of poliomyelitis by weeks in Kent. A central dot indicates a reception area. Evacuation took place September 1—3.

The most interesting focus was in Kent. Diagram V gives the weekly incidence of cases notified between June and November 1939, in the county, differentiating certain areas, in each of which several cases occurred. In these six months 85 cases were notified, 53 *after* evacuation. Of these 53, 34 were notified from reception areas, but only 5 cases occurred in evacuees, though probably some 16,000 school children had been billeted in these reception areas. The diagram suggests that the outbreak was but little influenced by evacuation, though Kent received 56,000 evacuees of whom 38,000 were school children. This home-county outbreak may be compared with that in the more rural parts of Essex (157 cases) in 1938.

Diphtheria.—Previous to evacuation the incidence of diphtheria in England and Wales had been slightly lower than in 1938 and very slightly lower than the median value for the previous nine years. No disease caused more anxiety among receiving authorities, who feared that in most cases their children were probably less immune

than the evacuated city children, who might be expected to bring with them a considerable proportion of carriers and fresh strains of infection.

But the total number of cases of diphtheria notified in England and Wales in the four months subsequent to evacuation was only 16,436 compared with 23,948. In some areas there was apparently a virulent *gravis* type of infection, and severe forms of the disease were reported in Leicestershire [1] and in the Don valley in the West Riding in December. In the later autumn there was a small epidemic in Reigate [6], 11 of the 30 clinical cases were in evacuees, but the three deaths occurred in local children.

Strenuous efforts were made in some reception areas to immunize both native and evacuated children, but the difficulty of obtaining parental consent in the case of evacuated children hindered the progress of immunization in many areas. The highest recorded immunization rate must, I think, be that of Aysgarth R.D., where in the greater part of the area 97% of the children have been inoculated and in the

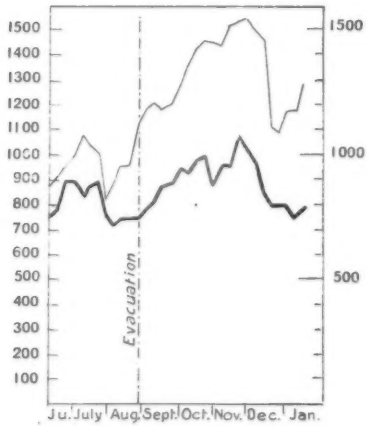

DIAGRAM VI.—Diphtheria, weekly incidence. Thin line — 1938. Heavy line — 1939.

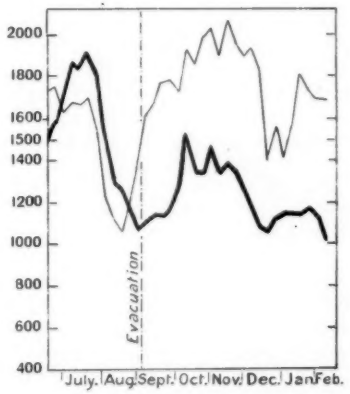

DIAGRAM VII.—Scarlet fever, weekly incidence. Thin line — 1938. Heavy line — 1939.

other portions over 75%. This achievement is the work of an energetic member of our section, Dr. W. M. Pickles.

Diphtheria however, more than most infectious diseases, is school-spread, and the complete closure of schools in the evacuation area, their partial closure in neutral areas, and the " double shift " with its half-time indoors school work in the reception areas may have helped to diminish the incidence, and to produce the very satisfactory state of things shown on Diagram VI as much as did the incomplete degree of immunization which was all it was possible to produce in most reception areas.

Scarlet fever.—Before evacuation there had been a comparatively high incidence of scarlet fever compared with the previous year, particularly in the evacuation areas ; thus in the week ending July 8 there were in London 203 cases (compared with 166 in 1938), Liverpool 64 (58), Manchester 50 (40). This high prevalence continued until the end of July, cases being then still well above the weekly average for 1938 in London, Birmingham, Hull, Leeds, Liverpool, Manchester, and Tottenham. There then was a rapid fall, and by the end of August the incidence was below the median of the last nine years. Towards the end of September there was a sharp rise

corresponding with the seasonal maximum in early November, but, as will be seen on Diagram VII, one that was very much less than the rise in the corresponding period of 1938.

The total cases notified during the four months after evacuation were 22,385 compared with 32,429 in the corresponding period of 1938. It must be remembered that considerable differences between consecutive years are by no means uncommon, but the high incidence of this disease had continued practically undiminished for several years, and there seems little doubt that the great changes produced by evacuation were on the whole favourable. In Eire and Northern Ireland, where there was no evacuation, notifications of scarlet fever were in excess of the figures recorded in 1938.

The fall in incidence was biggest in the great cities, where it was quite out of proportion to the number of children remaining in them. Thus, at the end of October, some 47% of the children were in London, but the cases of scarlet fever which occurred in London in that month were only 18% of those which occurred in the corresponding period of 1938, while the corresponding cases of diphtheria were only 23% of those in 1938.

In the four October weeks of 1939 there was only one diphtheria death in London compared with 14 in 1938.

Thus there were probably two main factors in the reduction of incidence following evacuation, the removal of susceptibles from the great cities and, more potent still, the effect of school closure on those left behind. In contrast to the comparatively low incidence of scarlet fever was a prevalence, obvious but of course unmeasured, of tonsillitis this autumn and winter—a prevalence which suggests that the prevalent strains of hæmolytic streptococci had lost toxigenicity rather than invasiveness.

Measles.—Measles was made notifiable from November 1. Up to the end of my period the expected epidemic seemed to be rather hanging fire, and still conspicuously avoiding the big cities and especially London.

Whooping-cough.—Whooping-cough was also made notifiable from November 1. There seems no evidence of any increase in incidence.

Rheumatic fever.—I have had no evidence of an increase in the civil population or evacuated special schools. Dr. Wilfrid Sheldon, who as pædiatrician in charge of a large children's hospital unit in a reception area, has had unusual opportunity for observation, has told me that he has been impressed by the almost complete absence of cases of *chorea*.

Undulant fever.—The fact that no increase has been reported seems worthy of mention as so many children have been evacuated from cities where they had had all milk pasteurized (either designated or commercially) to areas where the milk was untreated. Children, of course, do not appear very susceptible to this disease.

Pneumonia.—The incidence of pneumonia was lower than that of 1938 throughout the period under review. At the very end of the period it rose suddenly, the increase being probably attributable to influenza, as was shown by the concurrent increase in deaths ascribed to that disease.

Puerperal pyrexia.—Some 2,729 cases were notified in the four months subsequent to evacuation in England and Wales compared with 2,871 for the corresponding period in 1938.

That this period of the year, which includes the seasonal maximum, should show any decline in the notifications of the disease after so considerable a migration of expectant mothers, reflects no small credit on the arrangements made by the Ministry and the local health authorities, which have already been described. There was an almost complete freedom from any cases of institutional sepsis.

The fact that the emergency maternity homes were always amply spaced, as only some half of the expectant mothers who had signified their intention of going actually went to the reception areas, may have contributed to this happy result.

Minor infectious diseases.—A very extensive epidemic of *German measles* began with the close of the period, which had begun with one of *chicken-pox*. Both epidemics were of the usual mild character, but neither disease is notifiable and my scanty information is derived from hearsay and returns from nursery and special schools.

Mortality from Certain Infectious Diseases

The following table, which relates only to the months October, November, and December, shows that while deaths from scarlet fever and diphtheria have not decreased in the same proportion as have the notifications, yet, nevertheless, there is a substantial reduction.

The decrease in deaths from diarrhœa and enteritis under 2 years is substantial.

DEATHS FROM CERTAIN INFECTIOUS DISEASES—ENGLAND AND WALES.

	Last quarter 1938	Last quarter 1939	Percentage reduction 1938 = 100
Scarlet fever	64	47	27
Diphtheria	670	566	16
Enteric fever	41	27	34
Diarrhœa and enteritis under 2 years	797	582	27

Evacuated special schools.—I have examined the records of the health of 2,568 evacuated " special " school children housed in 15 different camps, &c.

Whilst these records are very rough, they are sufficient to convince me that the children have been extraordinarily free from infectious disease and indeed from any sickness. This is probably due to the fact that four-fifths of the children were housed in " chalet " holiday camps of a more or less permanent character. In these the children sleep in very small units, admirably adapted to limit the spread of any infection.

Evacuated nursery schools.—Dr. Dorothy M. Llewellin has been good enough to collect similar records from 17 nursery schools and day nurseries relating to 889 young children and infants, housed in 15 large country houses and one camp. Though naturally suffering more than the older " special " school children, the experience was, on the whole, fortunate. Measles only occurred in one of the 17 schools where an attack rate of 67% occurred. Whooping-cough occurred in five establishments, but there were only 30 cases in all. Epidemic diarrhœa (88 cases in all) occurred in four. Scarlet fever (32 cases in all) occurred in two ; and diphtheria (11 cases in all) also in two.

B. Contagious Diseases

Scabies had been on the increase in many evacuation areas for the past three or four years, but on the whole, the incidence reported from the reception areas was less than had been anticipated.

Impetigo, on the other hand, caused more trouble than was anticipated, and, in the early days of evacuation, came only third to pediculosis and enuresis as a cause of trouble.

Pediculosis.—It had not been generally appreciated, though shown year by year in the tables of the Annual Report of the Chief Medical Officer, that some 10% of elementary school children are still " found unclean " each year, although great reductions have been made in recent years. In most of this 10% the infestation is only to the extent of one or a few nits. The distribution of children found unclean is very uneven, some areas and some schools being always worse than others. In every large city there are such areas and schools in the older, poorer, and overcrowded parts, and, in the " zoned " (i.e. partially evacuated) cities, these were almost invariably

included in the evacuated zone. It was expected, therefore, that the incidence found amongst evacuated children would be higher than the average figure. Cleanliness can only be maintained in a clean home whatever the exertions of the school medical service, and the essential facts, first that pediculosis is a family disease; secondly that evacuation took place at the end of the summer holidays; and lastly, that all the health services in the evacuation areas had given, by Government direction, complete priority to preparations for civil defence, must be remembered. Moreover,

> "A clear distinction should be drawn between infestation with body and head lice. The former is a true measure of neglect and degradation. The eradication of the head louse from girls is a much more difficult problem and indicates particular rather than general negligence, however reprehensible it may be" [11].

Those reception authorities who had prepared to deal promptly with the cleansing of children, and to tackle cases of infestation before it became severe, had, as a rule, little difficulty, but unfortunately the children from some of the more heavily infested areas often arrived in rural areas with small staffs and little experience of the condition; in such cases infestation naturally progressed rapidly.

The main causes of the high incidence of infestation were:—

(1) Evacuation at the end of the summer holidays meant that no child had been inspected by the school nurse for four (and usually more) weeks; it was not found practicable by the evacuation authorities, immersed as they were with civil defence preparations, to inspect the children before they left.

(2) Previous ideas of infestation in school children were derived from inspections, of which notice is given to parents. For these, children are generally prepared, and this preparation, though right and proper, naturally leads to some cloaking of the normal condition. The official returns, therefore, are underestimates and, moreover, are averages.

Mr. Kenneth Mellanby, at a recent meeting of the Royal Society of Tropical Medicine, produced figures relating to the incidence and degree of infestation of children admitted to fever and other hospitals. These showed a much higher incidence than did the school medical service of the area from which the child patients came. Mr. Mellanby is continuing his investigations on behalf of the Board of Education and the Ministry of Health.

(3) The foster-mothers in the reception areas often did not understand that many children in towns cannot escape habitually harbouring one or two nits; at home the mother combs the hair nightly, and the infestation is thus kept down to almost invisible limits, but is not eradicated. If the child's head is left uncombed for a few nights, infestation rapidly becomes serious. In many a rural receiving area combing and the necessary fine-tooth comb were alike almost unknown.

Ringworm.—The very small number of cases of this disease reported in evacuees, an almost complete absence in fact, is a remarkable tribute to the school medical service, as anyone who remembers its incidence twenty years ago can tell.

Enuresis.—This troublesome problem, sometimes organic but generally psychological, has already been fully discussed by other Sections of this Society under the guidance of Dr. Hector Cameron [10] and other eminent authorities, so that I need not do more than mention it.

Summary

To sum up, the evacuation, incomplete as it was, moved and billeted in four days with wonderful success and punctuality, a number of persons ten times as numerous as the original expeditionary force. Moreover, hundreds of thousands of rural homes had new inmates, who might disturb familial immunity with new strains of infection, and the daily lives of millions of school children, besides those evacuated, were completely altered by school closure and the double shift. Many day, special,

and nursery schools became residential schools. Evacuation thus presents subjects of great interest to epidemiologists.

In the absence of an immediate air attack, which would probably have amply justified the measures taken, exaggerated criticism on other points seems to have entirely obscured the fact that the record of the first four months as regards infectious disease was extraordinarily good.

If, as a basis of comparison, this period is contrasted with the same four months in the previous year, the following remarkable facts emerge. The number of cases of diphtheria and scarlet fever respectively fell to two-thirds of those which occurred in 1938, and the cases of poliomyelitis only amounted to just over one-third, although all are diseases most prevalent in autumn, to which school children are peculiarly liable.

The slight comparative increase in the cases of enteric fever notified during the period was due to epidemics which began before evacuation took place, and which had little relation to it, though they continued in the weeks immediately following it. There was a decline in the notifications of puerperal pyrexia, compared with the last four months of 1938.

Diphtheria and scarlet fever showed little sign of declining incidence before evacuation, and this relative freedom from infectious disease must, I think, be due to other factors. First, it seems to me, to the careful preparation and hard work of the Evacuation Department of the Ministry of Health, and the Public Health Services, ably seconded by the domiciliary medical services ; the devotion of teachers and school nurses ; the generous care so often shown by the foster-parents ; and Nature's gift of a glorious autumn. It is evidence too, of the basic soundness of the environmental hygiene of this country.

Some other things too, which seemed so darkly to cloud the success of evacuation, had epidemiologically their silver linings ; the failure of half the " expected " number to go ; the rapid drift-back, which relieved overcrowding, facilitated appropriate billeting, and left in the reception areas those children most suited to country life ; the " double shift " schooling, which ensured for both native and evacuee children double their usual time in the open air, and allowed the natives to acquire by small and intermittent dosage some immunity to any fresh strains of infection their new companions might bring.

Even the much-deplored school closure in the evacuation and neutral areas helped to reduce the cases of diphtheria and scarlet fever by lessening the risk of school infection.

But when all this has been said, the record, in my view, proves the soundness of the policy of *dispersal*, not only against air attack, but dispersal in billets as a policy against the spread of air-borne disease. Those in search of some experimental analogy may refer to the work of Greenwood, Topley, and their colleagues (1936) [4]. All previous experience suggests that a policy of *concentration* of children in camps, which, although quite impossible on practical and financial grounds, has been recommended by some, would have produced a far less satisfactory picture as regards infectious disease, had it been generally adopted.

As regards contagious disease, the record is less satisfactory, and as regards pediculosis disappointing.

The evacuated children, who remain in the reception areas, have benefited enormously in health. In epidemics which have arisen since the new year and the close of the period under review, it is generally reported that they have shown more immunity and far better attendances at school than the native children. Many of those who returned home after some months in the reception areas still show the stimulating effects on growth and well-being.

In conclusion I have to thank Mr. G. A. N. Lowndes and Mr. I. G. Davies of the Ministry of Health for their invaluable help, their inexhaustible store of information and patience. I have had kind help, too, from Dr. Percy Stocks, Dr. Dorothy M. Taylor, and Dr. Constant Ponder, County Medical Officer for Kent, while Dr. Dorothy M. Llewellin has given me much information with regard to the incidence of infectious disease in evacuated nursery schools. I gratefully acknowledge my indebtedness to the weekly returns of the Registrar-General; to the admirable digests of them in the *British Medical Journal*; and to many epidemiological references in the *Lancet*.

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Clinical Section

President—DUNCAN FITZWILLIAMS, C.M.G., F.R.C.S.

[*April* 12, 1940]

Carcinoma of the Breast.—DUNCAN C. L. FITZWILLIAMS, C.M.G., F.R.C.S.

C. J., female, aged 36.

March 1931 : She had a lump in her left breast in the upper and outer quadrant. A radical amputation was performed. The mass was found to be a carcinoma. June 1931 a radium plaque was applied to the chest and surface radiation (17,670 mgm. hours) was given.

She has been under constant observation since and one or two glands have been felt in the axillæ from time to time.

April 1936 : A gland in the axilla was thought to be suspicious ; she was readmitted and the gland removed. It was not malignant.

She is quite well to date. Long survival after carcinoma at such an early age is extremely rare.

Recurrent Tumour in a Case of a Sarcofibroid of the Small Intestine, removed in 1937.—E. M. FRAENKEL, D.M.

The patient, a man aged 66, was first seen on April 28, 1937.[1] He complained of severe cramp-like pains in the abdomen extending round the waist, lasting one to three minutes and without relation to meals. He had lost weight and appetite and was constipated. The stools were black. The symptoms had first appeared at the age of 38 when diarrhœa in bouts of three to four days occurred, and the trouble recommenced thirteen years ago after an interval of fifteen years, becoming worse three months before he first saw me. He had lost 22 lb. in weight and after exertion felt weak and tired and giddy. He had stopped smoking and alcohol.

On examination.—The patient was anæmic and emaciated. Blood-pressure low. Tongue furred. No tumour or enlarged glands felt in abdomen or elsewhere. Stools contained occult blood but no red blood cells.

Blood-count : R.B.C. 3,190,000 ; Hb. 47% ; C.I. 0·8 ; W.B.C. 7,000.

He was admitted to Westminster Hospital because a tumour in the intestinal tract was suspected, but X-ray examination and sigmoidoscopy gave negative results. Fractiona l test meal showed complete achlorhydria.

Two blood transfusions were given and on June 24, 1937, laparotomy was performed by Mr. Stanford Cade under spinal anæsthesia (Mr. MacGill). The X-ray plates were reviewed before the operation and by the exclusion of all other possibilities a malignant tumour of the small intestine was diagnosed. At operation a large intussusception of the small gut was found which was easily reduced. In this part a large tumour was found within the lumen of the intestine and this was resected within a margin of healthy tissue. An end-to-end anastomosis was performed. No

[1] See *Arch. Ital. Chir.*, 1938, **52**, 154.

metastases were found and the abdomen was closed. Apart from some trouble from the spinal anæsthetic the convalescence was normal, the patient recovered his full strength, gained 10 lb. in four months, and the blood-count became normal.

The tumour was a broad-based submucous polypoid within the lumen of the small intestine, containing hæmorrhages in some parts. Part of the tumour showed a picture of a leiomyoma (Dr. Pulvertaft), but in another part the appearance was rather that of sarcoma cells such as Bland-Sutton described under the name of "sarcomatous fibroid".

The patient was not seen again for two and a half years, and then returned complaining of pain in the right side. He now shows a certain degree of anæmia and there is a large round tumour in the right upper quadrant. No glands can be felt but there are about 30 angiomata of about the size of a pea in his skin, not previously observed.

Blood-count: R.B.C. 3,675,000; Hb. 78%; W.B.C. 5,200.

The patient has lost 7 lb., now weighing 9 st. 13 lb.

No liver dysfunction is shown by the lævulose tolerance test. Urinary diastase: 22 units. Urinary melanin absent. No occult blood from stools. Blood sedimentation rate: 5 mm. in one hour and 9 mm. in two hours.

The treatment is conservative and the diagnosis that of a cyst or a recurring tumour (sarcoma ?) arising from the retroperitoneal tissue.

Four Cases of Familial Endocrinopathy.—HAROLD AVERY, M.D.

Two Brothers with Graves' Disease.

(1) J. R., aged 25, complains of "nervousness", sweating, loss of weight, and palpitations. He cannot bear heat or sun and once fainted in the heat. At the age of 16 he had a "nervous breakdown" and was away from school for two months.

Examination reveals all the classical signs of Graves' disease: exophthalmos (slight), Von Graefe's sign, tachycardia (104), tremors, exaggerated reflexes.

(2) L. R., aged 22, brother of J. R., gives a similar history and shows similar physical signs. He is doing well on treatment by rest, bromides, and belladonna.

Two Brothers with Dissimilar Endocrine Disease.

(3) A. S., aged 23, gives a history of flushes, sweats, and "nervousness" during the past twelve months. He has palpitations and dyspnœa on exertion. He has lost a stone in weight in the last nine months.

At the age of 3 years he had diphtheria; chorea at 19, and scarlet fever at 21.

Examination shows a flushed perspiring skin, fullness of the neck, exophthalmos, and Von Graefe's sign. Pulse-rate 110. Tremors of the outstretched fingers. All reflexes are very brisk.

(4) R. S., aged 26, brother of A. S., complains of shortness of breath and palpitations on exertion, sleeplessness, abdominal discomfort after food, and occasional vomiting. There is frequency of micturition, ten or more times during the day and two or three times at night. He has been steadily increasing in obesity since the age of 15 though he does not eat sugar, sweets, or chocolates, and diets himself.

He is a stocky man with marked obesity of the hypopituitary type. The penis is small and buried in the pubic fat. The testes appear to be normal.

Steatorrhœa with Radiological Changes in Vertebrae.—R. S. BRUCE PEARSON, D.M.

D. E., male, aged 14½ years.

Has complained of diarrhœa for three to four months with sudden onset. He has lost a good deal of weight and has recently been drinking large quantities of fluid.

Complains of no pain or cough. Has recently had occasional frequency of micturition. He now passes a fluid motion two to three times daily. Previous illnesses: measles and chicken-pox.

On examination.—Weight 6 st. 2 lb. He has a high complexion and is rather thin. Heart and chest normal. Abdomen prominent with flattened umbilicus and doughy feel on palpation. Stools on a mixed diet were greyish, frothy, and liquid; no blood or pus was seen, but on one occasion a large mucous cast of the colon was found. On a fat-free diet, stools are watery. Occasional irregular temperature up to 99·5° F. Chvostek and Trousseau signs negative. Spine moves freely and painlessly.

Investigations.—Fæces: No pus, red cells, or occult blood found. There were occasional meat fibres without striations; no starch granules seen. On several occasions excess of fat has been observed. On a mixed diet, total dried fat 83·1% of dry weight (37·8% split, 45·3% unsplit). On a low-fat diet, total fat 27·6% dried weight (15·6% split, 12% unsplit). No abnormal organisms in stools. Agglutination tests negative to typhoid para A and B.

Mantoux test negative to 1 : 1,000, 1 : 100, 1 : 10.

Blood sedimentation rate 4 mm. per hour.

Blood.—Hæmoglobin 94%. (83·5% polys., 12% lymphos., 3·5% monos., 1% eosinophils.) Serum calcium 6 mgm.%. Serum protein 2·9 grm.%. Serum albumin 2·8 grm. %. Serum globulin too small to estimate. Cholesterol 92 mgm.%. Serum phosphate 4·5 mgm. Serum phosphatase 8·6 units. Serum urea 32 mgm.%.

Fractional test meal showed complete achlorhydria, emptying within one hour. No free hydrochloric acid after histamine injection.

X-ray investigations.—Chest normal. Alimentary tract: terminal ileum closely applied to ascending colon. Some delay in passage of meal into the cæcum. Suspicion of plastic peritonitis with matting of small gut round the cæcum. Spine: partial collapse and erosion of TV.7 and some erosion of TV.11. Other vertebræ showed similar but less marked changes. Appearance suggests osteochondritis.

Electrical reaction of muscles: No abnormality.

Rheumatoid Type of Arthritis (Still's Disease) Treated by Splenectomy.—FRANCIS BACH, M.D.

B. L., female, aged 18.

History.—When aged 14, pain in the right ankle, spreading within six months to knees and hands with swelling of these joints. Had to give up her work, which was sewing. In-patient at the Orthopædic Hospital, Stanmore, for one year. She had ten injections of gold, and extension for the knees, followed by out-patient treatment.

The condition remained unchanged until three months before admission to St. Stephen's Hospital Rheumatic Unit, in June 1939, when there was a recurrence of pain and swelling in the knees and wrists, and she was unable to walk.

Past history.—Nothing definite.

Family history.—Three brothers, all healthy.

On admission to the Rheumatic Unit general condition fair, but unable to get about without very great difficulty. Contraction of fingers; marked swelling of both wrists. Both knees swollen and painful on movement with wasted quadriceps muscles. Left ankle stiff, toes contracted. Enlarged glands in anterior triangles of neck and epitrochlear regions. Tip of spleen palpable on several occasions. No cardiac enlargement; heart sounds normal; blood-pressure 130/80; rate 80.

Investigations.—Sedimentation rate raised. Tuberculin patch test negative. Skiagram of wrists showed destruction of carpal bones.

Wassermann reaction negative. Kahn negative. Gonococcal fixation test negative. Blood-count: R.B.C. 4,680,000; Hb. 82%; C.I. 0·8; W.B.C. 10,700.

Test meal : hypochlorhydria. Blood culture sterile. Right knee aspirated. Sticky yellow fluid containing polymorphs and lymphocytes. Culture sterile.

Treatment.—On admission, neo-solganal injections given weekly, but these had to be discontinued as albuminuria occurred. Vaccine made from fluid aspirated from the knee-joint ; injections given weekly in increasing doses for four months ; no reaction ; no improvement in joint condition. General medical and physical treatment was followed by some improvement in general health but no improvement in joint condition.

8.11.39 : Splenectomy performed by Mr. K. F. D. Waters. Weight of spleen 171 grm. Spleen bound down to diaphragm and posterior lateral abdominal wall by broad short adhesions.

Histological report : This spleen shows a very marked degree of amyloid degeneration. The process is principally related to the Malpighian bodies.

Result.—Definite improvement in general health and marked improvement in condition of affected joints.

Comment.—At a meeting of the Royal Medical and Chirurgical Society in 1896 Dr. George Still read a paper on " A Form of Chronic Joint Disease in Children ". He described a form of chronic polyarthritis of childhood beginning before the second dentition and characterized by chronic progressive enlargement of joints, without bony change, and by general enlargement of the glands and of the spleen. In 1924 Dr. A. R. Felty published a paper in the *Johns Hopkins Hospital Bulletin* entitled " Chronic Arthritis in the Adult associated with Splenomegaly and Leukopenia ". He presented his patients as examples of a distinct clinical entity of " unknown origin ". They were apparently suffering from a rheumatoid type of arthritis similar to Still's syndrome. In 1930 Dr. Paul Chevallier emphasized the similarity of the Chauffard-Still syndrome to " Le Rheumatisme Bilaire " and the arthritic manifestations of " biliary cirrhosis ". He noted that in patients with splenic enlargement, the associated symptoms often abate after removal of the spleen, but that, so far as he knew, in no instance had the spleen been removed in the Chauffard-Still syndrome. In 1932 Dr. Hanrahan and Dr. Miller reported the result of splenectomy in a middle-aged woman presenting the Felty syndrome. In 1934 Dr. Craven reported a similar case. In 1937 Dr. Loeper and his colleagues removed the spleen of a young woman, 28 years of age, suffering from an advanced rheumatoid type of arthritis. They noticed marked improvement in the general health and return of function in the affected joints immediately following treatment. Later in 1937, Dr. Villaret presented a similar case. Bach and Savage (1940) say : " It is well known that surgical intervention, such as tonsillectomy or cholecystectomy, for the removal of foci of infection in patients suffering from the rheumatoid type of arthritis may be followed by transient improvement. Some temporary diminution of pain and joint deformity may occur. Whether this is due to the removal of a specific causative factor, or to the production of non-specific protein shock with stimulation of the reticulo-endothelial system, or to the period of rest and controlled diet that follows an operation, we do not know."

Splenectomy should only be considered in severe and advanced cases where usual treatment has failed.

Discussion.—Dr. PARKES WEBER pointed out that in commenting on a case of Chauffard-Still-Felty syndrome (*Proc. Roy. Soc. Med.*, 1938, **31**, 474) he had called attention to a report in the *Presse Médicale*, January 15, 1938, p. 85, of two cases discussed at the Algiers Medical Society of the Chauffard-Still-Felty syndrome, in which splenectomy had been performed. He asked in how many of Dr. Bach's cases amyloid changes had been noted, and if the spleen was enlarged in every case.

Dr. BACH : I would say that three out of five of my cases have shown amyloid changes in the spleen, and I have looked for amyloid changes in the kidneys as well. Both gold injections

and drastic operative procedure (such as splenectomy) may be contra-indicated when such changes are present. Professor Ernst Freund, of the Pearson Institute, examined the urine of four of my patients to detect clinically early amyloid changes in the kidneys; the result was positive in two and negative in two. There has been no mention of amyloid disease in the description of the spleens that have been removed either in America or in France.

The decision as to whether splenectomy is justifiable depends not on whether the spleen is enlarged but on the degree of joint changes and the failure of response to other methods of treatment. If every other method has failed and the patient appears to be a hopeless cripple, I am prepared to consider splenectomy even though the spleen is not palpable. However, in all my cases the spleen has been palpable.

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Chronic Splenomegaly of Uncertain Causation.—F. PARKES WEBER, M.D.

The patient, C. H., aged 67, is a man of medium general nutrition, still working as a stove-fitter. He has noticed a definite swelling in the left portion of his abdomen, and for the last four years has complained of a good deal of cutaneous pruritus, especially of his legs when warm in bed. The abdominal swelling is due to a smooth rather hard enlargement of the (typically notched) spleen, which reaches down to the level of the anterior superior iliac spine and to within an inch of the umbilicus. By radiographic examination (1939) the stomach appeared displaced to right, as if by splenomegaly. There is no enlargement of the liver, or of the superficial lymph glands, excepting slight in the groins—possibly connected with the chronic pruritus and scratching of his legs. During the last twelve months he has had occasional pains in the region of his enlarged spleen (? perisplenitic).

Blood-count (April 9, 1940): R.B.C. 4,800,000; Hb. 93%; C.I. 1·0; thrombocytes 140,000; W.B.C. 8,300 (eosinos. 6%; polymorphonuclear neutrophils 68%; lymphos. 23%; monos. 3%); slight poikilocytosis; no nucleated red cells; about 18 reticulocytes in 1,000 red cells.

The patient has been under observation for the last year and repeated blood-counts have been taken. These have often shown a little poikilocytosis and anisocytosis, and one or two nucleated red cells, metamyelocytes or myelocytes; on one occasion a perfect megakaryocyte was observed; on another occasion the eosinophilia was up to 8%. Sternal puncture suggested somewhat over-active hæmopoiesis (both on red and white sides), but otherwise nothing abnormal. Urine: faint trace of albumin. Blood-Wassermann reaction and Pirquet cuti-reaction, negative. Nothing abnormal has been found by other general and special examinations, including radiogram of thorax, electrocardiogram, fractional tests of the gastric contents, erythocyte-sedimentation rate, blood-pressure, ophthalmoscopic examination, and examination of the patient's scanty sputum for tubercle bacilli. There is no abnormal

" fragility " of erythrocytes ; hæmolysis commences with the 0·50% sodium chloride solution and is complete with the 0·46% solution.

The patient is apparently not losing weight ; his weight now is 50·8 kilograms (8 st.). He has slight varicose veins of lower limbs. No family history of importance. Thirty years ago he had an attack of left facial paralysis, of which he still shows remains.

In regard to diagnosis it should be noted that the splenomegaly was observed when he was under hospital treatment for duodenal ulcer in March 1927, but according to the patient it was noted first by Dr. L. A. Smith about 1921, when he was examined (for " weakness ") at the London Hospital. It seems to have increased somewhat during the last year. He never had malaria and has never been out of England. A possibility is that it is due to an unusual chronic form of Hodgkin's disease or allied reticulosis. (The chronic pruritus and occasional slight blood-eosinophilia would be in favour of such a diagnosis.) Could it have been caused by thrombosis of the splenic vein of unknown causation, or is the case one of non-leukæmic myelosis of the spleen (erythroblastic and megakaryocytic splenomegaly) ?

At the meeting Dr. B. Kounine has suggested to me that the splenomegaly might be due to an atypical form of erythræmia (Vaquez-Osler polycythæmia). Though our numerous blood-counts have never shown any polycythæmia, the total volume of the patient's blood might nevertheless be increased. In favour of Dr. Kounine's suggestion are : (1) the habitual facial rosacea and the tendency to conjunctival hyperæmia ; (2) frequent feelings of giddiness ; (3) the rather slow erythrocyte-sedimentation (this should be accelerated, were the splenomegaly due to Hodgkin's disease) ; (4) the thinness of the patient. One point against the suggestion is that there is no increase of the white cell count.

Dr. B. Kounine : But for the normal R.B.C. the patient strikes one at first glance as a typical case of polycythæmia. The highly coloured cheeks, nose, forehead and chin, as well as the patient's complaints, are all in conformity with this diagnosis. The symptoms of giddiness, feeling of heat, pruritus aggravated by warmth and alleviated by cold, are those of a definite vasomotor disturbance commonly met in polycythæmia. To these should be added the usual sensation of pain in the splenic region. The differential W.B.C., as well as the low blood sedimentation rate, fit in with the picture of polycythæmia.

Roger S. Morris [1] has described two cases of " anerythraemic erythæmia " in which he found a splenomegaly and the remaining signs and symptoms of a polycythæmia except the actual increase in the number of erythrocytes.

It has been observed that in polycythæmic patients a difference in the R.B.C. of 2–3 millions may be found merely as a result of a few days' rest or even for no obvious reason at all. It is this marked fluctuation in the R.B.C. rather than the actual increase of the number of the erythrocytes which constitutes, in my opinion, the distinguishing feature of polycythæmia vera.

Reference.—[1] *Johns Hopkins Hosp. Bull.*, 1910, **21**, 37–40.

Ulcer in Connexion with Congenital Keloid of Leg, treated with Abdominal Tubed Pedicle Graft.—D. N. Matthews, F.R.C.S. [*Case shown March* 7, 1940.]

R. S., male, aged 13 years. This boy was shown before the Clinical Section in February 1934 and again in April 1936 (*Proceedings*, **27**, 631, Clin. Sect., **53** ; **29**, 1219, Clin. Sect., **29**). On the first occasion the condition was discussed and the rarity of congenital keloid emphasized. A suggestion was made that it would be worth while to excise a part of the lesion and to cover it with a Thiersch graft. This was done with temporary improvement, but the keloid and the ulceration both recurred. In order to improve the blood supply a lumbar sympathectomy was also performed, and it was after these attempts at cure that he was shown for the second time (1936).

By January 1938 the condition of the leg was found to be worse than before treatment, the keloid extending from the ankle to the middle of the thigh. A severe contracture of the knee had developed as a result of the keloid and its underlying fibrosis, which was quite an inch thick. A large ulcer was present below the knee and stretched almost from the knee to the ankle.

It was decided therefore to raise an abdominal full-thickness graft and convey it by stages to the back of the leg. It was realized that it would be impossible to cover the entire keloidal area and it was decided that the ulcerated lesion below the knee should receive the graft.

FIG. 1.—Before treatment. Showing ulcer and fixed flexion of knee.

FIG. 2.—After treatment. Showing graft over ulcerated area and full extension of knee.

Technically the procedure was difficult as any attempt to attach the new skin to a keloidal area resulted in its immediate rejection, the keloid treating the pedicle as a foreign body and making no attempt to unite. On two occasions all stitches cut out and the pedicle became detached. Sepsis always developed around the stitches at every move, and I think the graft was saved on several occasions by the instigation of pre-operative prontosil therapy before each operation.

It was noticed that the skin in the neighbourhood of the foot greatly improved as soon as the tube was attached to the leg, which was probably due to the increased blood supply to the part.

He now has a healed leg and a knee-joint in which the range of movement is full, but there is still some excessive fibrosis on the outer side of the thigh. This may need further excision at a later date but is still improving. Much cosmetic improvement is still possible and will be undertaken when the graft has had several months in which to settle down.

Discussion.—Dr. PARKES WEBER expressed his opinion, as he did when the patient was first shown, that the case was originally one of *linear morphœic sclerodermia*. He did not believe that a congenital keloid line, reaching downwards along the thigh as far as the ankle, was known to exist.

The PRESIDENT said that like Dr. Parkes Weber, he had seen congenital bands down the back of the thigh but he did not regard them as keloid. He did not believe there was such a thing as a congenital keloid. Years ago he had conducted an investigation on thousands of babies noting the condition of their vaccination scars as these were the sort of injuries which produced keloids. He had also written to many vaccination officers. He had never seen a keloid in a baby nor had he ever heard of anyone else having seen one. From this he drew the conclusion that young children could not develop keloids.

Section of Therapeutics and Pharmacology

President—Sir WILLIAM WILLCOX, K.C.I.E., C.B., C.M.G., M.D., F.R.C.P.Lond.

[*December* 12, 1939, *continued*]

Reactions Induced by Intradermal Injection of Rheumatic Joint Fluid : Neutralization by Convalescent Sera

By C. A. GREEN

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INTRODUCTION

ALTHOUGH acute rheumatism is frequently associated with streptococcal infection, the joint fluid in rheumatic arthritis is usually found to be sterile. Of the exceptional observations may be mentioned the work of Richards (1920), and of Billings, Coleman and Hibbs (1922), who reported the isolation of streptococci in cultures of joint fluid. Cecil, Nichols and Stainsby (1929), in addition to recovering attenuated hæmolytic streptococci from blood cultures in a large series of cases, found the same organism in some of the joint lesions. Examination of stained smears of joint fluid shows, in the main, polymorphonuclear leucocytes in various stages of destruction. Organisms can rarely be detected, but the occasional finding of Gram positive cocci has been reported by Graff (1936) and by Poynton and Schlesinger (1937). Clinically, the joint pains in acute rheumatic fever are fleeting in character, and the joints are rarely left with permanent damage after the initial attack. In these respects, the arthritic lesions appear to be due to some transient toxic action, rather than the result of actual tissue invasion.

Green, Glazebrook, Thomson and Hopkins (1939) have shown that convalescent rheumatic serum had a beneficial action when given to certain cases of acute rheumatism, but was without effect in others. In successful cases there was a rapid fall in temperature and pulse-rate with relief of symptoms. The following observations were made in an attempt to find the mechanism of this action, and thereby to formulate a method for the selection of sera for therapeutic purposes.

METHODS

Removal and treatment of joint fluid.—Fluid was removed with aseptic precautions from an affected joint within twenty-four hours of the onset of symptoms by means of a wide-bore needle and syringe. The fluid coagulated overnight in the ice-chest, and on the following day partial separation had occurred. After centrifugation at 3,000 revolutions per minute for thirty minutes, the bulk of the supernatant fluid was removed, leaving 1 to 2 c.c. The supernatant fluid was stored at 6° C.

Sterility tests.—The coagulum and remaining supernatant fluid were mixed by shaking, and portions of the coagulum were then inoculated into the following media: Horse muscle digest broth, 10% human serum broth, 10% ox serum broth, 5% horse blood-agar and Loeffler serum. The chorio-allantoic membranes of ten-day-old fertilized eggs were also inoculated.

Intradermal tests.—Preliminary tests in rabbits and in guinea-pigs had shown that the intradermal injection of rheumatic joint fluid failed to elicit any visible skin reaction. The remaining tests were all performed in one human subject, using the separated supernatant fluid. The test subject A was a healthy male, aged 31 years, with no history of acute rheumatism. The results were read at twenty-four, forty-eight, and seventy-two hours, and recorded as the longest diameters in mm. of the zone of erythema.

Neutralization tests were made whenever possible. Sera were obtained at frequent intervals by venous puncture during various phases of illness, and kept without preservative at 6° C. Equal volumes of joint fluid and serum were mixed, incubated at 37° C. for four hours, and the test dose, 0·3 c.c. of the mixture, was then injected intradermally into subject A.

Results

The observations were made in the following cases of acute rheumatic fever :—

Case 1.—J. E. B., MX 57652. 485/39. Aged 16 years.

Family history.—No rheumatism.

Previous history.—Tonsillitis infrequent—no rheumatism.

Present history.—19.1.39 : Acute pain and swelling in both knee-joints, and elbow-joints.

20.1.39 : 10 c.c. convalescent serum intramuscularly.

24.1.39 : Temperature still raised—salicylate therapy started.

30.1.39 : Salicylates stopped following good reaction. No cardiac complication occurred ; patient was discharged to duty.

10 c.c. joint fluid was removed from the left knee on 19.1.39. The fluid was sterile as judged by our tests. After standing overnight in the ice-chest, 0·3 c.c. of the supernatant fluid obtained by centrifugation was injected intradermally into the forearm of subject A. After twenty-four hours the site of injection was surrounded by an area of erythema 40 × 80 mm. The centre of the reaction was brighter than the surrounding zone, the edge being quite distinct. After forty-eight hours, the area had increased to a maximum of 120 × 60 mm. and was tender and swollen. The bright coloration subsequently faded and the swelling decreased, but at the centre a small papule persisted for several days.

Specimens of sera were taken from the case J. E. B. during the first ten weeks of illness, and the effect of admixture of such sera on the capacity of the joint fluid to produce an erythematous reaction in subject A was determined. The results are given in Table I. It was noted that as a result of storage and incubation at 37° C. the activity of the joint fluid had deteriorated. The zone of erythema at forty-eight hours resulting from the injection of 0·3 c.c. of the stored fluid was 30 × 50 mm. (col. 6), as compared with 60 × 120 mm. in the case of the fresh fluid. The serum control (col. 7) indicated that the serum of patient J. E. B. was ineffective in subject A. Sera taken during the convalescence of the patient J. E. B. (col. 2, 3, and 4) had a definite neutralizing action in preventing the appearance of the erythematous reaction. On the other hand, serum taken on the day that knee-joint fluid was obtained, failed to neutralize (col. 1), although the zone of erythema was reduced as compared with the test dose of joint fluid (col. 5). The clinical data and sedimentation rates showed that the patient was acutely ill on 19.1.39, but was greatly improved on the days on which subsequent specimens of serum were tested.

Case 2.—K. B., 553126, aged 16 years.

Family history.—Nil relevant.

Previous history.—Nil relevant.

Present history.—5.4.39 : Complained of pain in both knee-joints and ankle-joints. Salicylate therapy started. On admission to hospital patient was sweating profusely. The left knee was swollen, tender, and inflamed. Heart-rate increased but no other abnormality. 20 c.c. convalescent serum intramuscularly.

8.4.39 : Knees and ankles still painful. Salicylates started.

10.4.39 : Joint pains ceased but temperature still 100° F.

14.4.39 : Pulse and temperature improving but joint pains returned. 20 c.c. convalescent serum.

5.5.39 : Cardiac impulse diffuse and double murmur now present.

15.6.39–17.6.39 : Sore throat, joint pains, and pericarditis. Temperature 103° F.

22.6.39 : 20 c.c. convalescent serum intramuscularly.

24.6.39 : Greatly improved and removed from dangerous case list.

During next three months there was periodical recurrence of joint and muscle pains, with development of mitral stenosis.

27.4.39 : 4 c.c. turbid yellow fluid were removed from the left ankle-joint within twenty-four hours of the onset of pain and swelling. Culture tests were all negative. The intradermal injection of 0·3 c.c. of the fresh fluid produced a reaction of 40 × 60 mm. in subject A. Specimens of sera were taken for neutralization and the results were as shown in Table II. The stored fluid had not deteriorated to any extent, since the reaction to 0·3 c.c. was only slightly smaller than that produced by the fresh fluid. In this case, however, any neutralization of the serum was not demonstrable by the cutaneous reaction, save for a doubtful effect of the serum dated 8.6.39 (col. 4). Clinically, this patient was in very poor general condition, with persistently abnormal erythrocyte sedimentation rate and formol-gel reaction. Later he developed pericarditis and was gravely ill.

Case 3.—J. G. J., aged 16 years.

Family history.—Nil relevant.

Previous history.—Nil relevant.

Present history.—30.5.39—31.5.39 : Onset and pain in back, both knees, elbows, and left ankle.

3.6.39—5.6.39 : Joint pains ceased following salicylate therapy, soft mitral systolic murmur present. Severe epistaxis.

10.6.39 : Moderate effusion into left knee-joint. For some days there was pain in joints of upper extremities.

Further convalescence uneventful.

11.6.39 : The left knee was tapped and 14 c.c. straw-coloured fluid obtained. Culture tests were all negative. On intradermal injection in subject A, 0·3 c.c. of the fresh fluid produced a reaction of 30 × 40 mm. and the stored fluid was equally effective (Table III, col. 6). In this case, there was evidence of neutralization in the serum dated 13.7.39 (col. 4), but not in earlier specimens.

Discussion

Our evidence suggested the presence of some toxic or irritative component in the joint fluid from cases of acute rheumatism, as all three specimens were sterile as judged by the cultural tests adopted. The appearance of the erythematous reaction produced by the injection of joint fluid was very similar to the Dick reaction. A single attempted neutralization test by means of horse antistreptococcal serum was not successful on account of the reaction induced by the serum alone. The erythematous reaction was demonstrable in the human subject and not in rabbits nor in guinea-pigs ; a fact in accordance with the observation that rheumatic fever cannot be transmitted experimentally to lower animals. So far only one subject has been tested for reactivity to these joint fluids, and there have been no untoward sequelæ.

As regards the properties of the toxin-like component, little information has been obtained because of the difficulty in working with a fluid of high protein content. Storage at 6° C., followed by incubation at 37° C., caused some deterioration.

The observation that sera in the later stages of convalescence developed the capacity to neutralize the action of the fluid whereas this did not occur at the onset

of infection, gave further support to the hypothesis that a toxin-like component was present. The neutralizing action of sera during convalescence was demonstrated in two of the three cases studied, and its appearance coincided with the clinical improvement of both patients. Case 2 was of much greater severity in that pericarditis supervened and no neutralization effect was demonstrable at any time the patient was under observation.

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Table I.—Reactions in mm. to Intradermal Injection in Subject A of Mixtures of Rheumatic Joint Fluid and Sera, From Patient J. E. B., after Incubation at 37° C. for Four Hours.

	Test				Controls		
	Col. 1 19.1.39 Serum + joint fluid	Col. 2 3.2.39 Serum + joint fluid	Col. 3 23.2.39 Serum + joint fluid	Col. 4 29.3.39 Serum + joint fluid	Col. 5 Joint fluid 1 test dose 0·15 c.c.	Col. 6 Joint fluid 2 test doses 0·30 c.c.	Col. 7 29.3.39 Serum 0·15 c.c.
24 hrs.	20 × 30	10 × 10	5 × 5	5 × 5	20 × 35	30 × 45	5 × 5
48 hrs.	20 × 25	0	0	0	30 × 40	30 × 50	0
72 hrs.	10 × 10	0	0	0	20 × 30	20 × 35	0

Table II.—Reactions in mm. to Intradermal Injection in Subject A of Mixtures of Rheumatic Joint Fluid and Sera, from Patient K. B., after Incubation at 37° C., for Four Hours.

	Test				Controls		
	Col. 1 26.4.39 Serum + joint fluid	Col. 2 3.5.39 Serum + joint fluid	Col. 3 18.5.39 Serum + joint fluid	Col. 4 8.6.39 Serum + joint fluid	Col. 5 Joint fluid 1 test dose 0·15 c.c.	Col. 6 Joint fluid 2 test doses 0·30 c.c.	Col. 7 8.6.39 Serum 0·15 c.c.
24 hrs.	25 × 25	20 × 25	25 × 25	15 × 15	25 × 30	30 × 40	5 × 5
48 hrs.	25 × 30	25 × 30	25 × 25	20 × 20	25 × 30	35 × 50	0
72 hrs.	25 × 30	25 × 30	25 × 25	20 × 20	25 × 30	30 × 40	0

Table III.—Reactions in mm. to Intradermal Injection in Subject A of Mixtures of Rheumatic Joint Fluid and Sera, from Patient J. G. J., after Incubation at 37° C. for Four Hours.

	Test				Controls		
	Col. 1 8.6.39 Serum + joint fluid	Col. 2 15.6.39 Serum + joint fluid	Col. 3 22.6.39 Serum + joint fluid	Col. 4 13.7.39 Serum + joint fluid	Col. 5 Joint fluid 1 test dose 0·15 c.c.	Col. 6 Joint fluid 2 test doses 0·30 c.c.	Col. 7 13.7.39 Serum 0·15 c.c.
24 hrs.	10 × 15	15 × 15	10 × 10	5 × 5	15 × 20	25 × 35	5 × 5
48 hrs.	10 × 20	20 × 20	10 × 10	5 × 5	20 × 20	30 × 40	0
72 hrs.	15 × 20	20 × 20	10 × 10	0	20 × 20	25 × 30	0

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Prophylactic Inoculation Against Whooping-Cough

By I. H. Maclean, M.B.

In whooping-cough, immunity, once acquired, usually lasts a lifetime. Second attacks of the disease have been reported but are rare. If each occurrence of a second attack was confirmed by cough plate culture or by complement fixation, the number of genuine second attacks would be even less.

Where a bacterial infection confers a lifelong immunity we expect to obtain good results from prophylactic inoculation. Vaccine therapy in whooping-cough has had its ups and downs since it was introduced by Bordet in 1909, but it has steadily gained favour as a prophylactic.

It is to be regretted that no field experiments have been carried out in this country on a sufficiently large scale, whereby our laboratory work could be led to its natural conclusion.

Up to 1930, most stock pertussis vaccines were made from old laboratory strains of *H. pertussis*, rough from cultivation on unsuitable medium. Leslie and Gardner (1931) described the S → R variation which takes place when strains of *H. pertussis* are grown for long periods on laboratory medium. In my experience, all newly isolated strains have smooth colonies and are fully virulent. These are the Phase I strains of Leslie and Gardner, who traced the degeneration of their newly isolated strains through various phases until they eventually reached Phase IV, the permanently rough state. Only Phase I strains were proved to be fully virulent in animal experiments. Antisera made against Phase I strains will completely agglutinate only Phase I organisms. Strains in the intermediate phases partly agglutinate with Phase I antiserum, but fully agglutinate against their homologous phase antiserum. Phase IV serum agglutinates only rough or avirulent strains.

Pertussis vaccine should be made only from strains which are in Phase I, and which are either newly isolated, or have been maintained in Phase I by growth on Bordet-Gengou medium. This brings it into line with other vaccines used in prophylaxis which are made only from strains of proved pathogenicity and potency. Vaccines are best made from cultures grown on media containing human blood. It is inadvisable to use animal blood, because the percentage of blood necessary to provide a good medium is so great that there is a danger of rendering the vaccinated person hypersensitive to the animal protein contained in the serum, and consequently in the vaccine also. This danger is particularly great if the subjects are children under 1 year of age, who may receive, under some schemes of dosage, as much as 8 c.c. of the vaccine during the course of immunization.

Lawson (1939) has confirmed the observation of Leslie and Gardner that only Phase I, or smooth vaccines, are capable of protecting mice. The following table has been adapted from Lawson's paper :—

Table I (after Lawson).—Showing the Difference between "Smooth" and "Rough" Vaccines in the Protection of Mice.

Dose : 3 weekly doses amounting in all to 4,000 millions.

Type of vaccine	No. of mice	% survivors
"S" vaccine, Phase I	29	71
"R" vaccine, Phase IV	27	7·5
*Undenatured bacterial antigen ..	23	0
Controls (full dose)	18	5
Controls (half dose)	12	0

*Arbitrary dosage, strength unknown.

Undenatured bacterial antigen is a watery extract of ground-up *H. pertussis*, prepared according to the method of Krueger, *et al.*, 1933.

Thus the "S" vaccine gave nearly ten times as much protection as the "R" vaccine, while, in this experiment, undenatured bacterial antigen gave no protection.

Most of the recent work on the prophylaxis of whooping-cough has been done with vaccines made from strains of Phase I. The literature of the last nine years contains records of some twenty thousand children who have been inoculated against pertussis, and the attack rate in most cases was under 5%. About one-tenth of those inoculated are suspected of having intimate contact with the disease subsequent to the completion of their immunization course. The communicability rate is the percentage of the exposed children who eventually contract the disease. It shows an approximate average in the inoculated children of 10%, compared with a communicability rate in controls from 60 to 90%, according to the severity of the epidemic. It is perhaps significant that the communicability rate in both inoculated and control groups rises steadily with the intimacy of contact and exposure, showing that artificially acquired immunity, like the natural immunity, is only relative. Inoculation greatly modifies the course of the disease, and all but a small percentage of cases in the inoculated group are classified as mild or atypical. Many of the cases appearing in the inoculated groups would not have been identified as whooping-cough had there not been a most rigid follow-up system. These results compare very favourably with those reported recently from the use of vaccines in prophylaxis against *B. typhosus* and the meningococcus.

In Table II some of the more important results of field experiment in U.S.A. and Canada and elsewhere are recorded. The list is by no means complete, because of the difficulty in comparing the results of so many different workers, but it includes the successes as well as some of the reported failures.

TABLE II.—SUMMARY OF CONTROLLED PERTUSSIS PROPHYLAXIS.

	Test group					Control group			
Author	Dose 1,000 M.	No.	Exposures	Cases	%*	No.	Exposures	Cases	%*
Madsen,† 1929 ..	22	1,832	Epidemic	1,347	75	446	Epidemic	438	98
Silverthorne, 1938 ..	120	747	91	1	1	161	27	23	85
Kendrick, 1939 ..	80	1,815	415	52	13	2,397	508	348	69
Miller and Faber, 1939	80	211	29	9	31	182	32	29	96
Sauer, 1939	80	2,453	—	32	—	1,730	—	286	—
Singer-Brooks, 1939	80	272	42	7	16	256	71	62	87
Doull, &c., 1936 ..	80	483	—	61	—	496	—	71	—
Seigel, &c., 1937 ..	80	101	17	9	52	110	47	22	46
Maclean,‡ 1939 ..	16–20	513	46 known	0	0	154	115	89	77
			45 suspected	0	0	—	—	—	—

* The percentage of known exposures who were attacked with the disease.

† Madsen worked during an epidemic, so that most of his cases were exposed to infection before immunity had time to develop. His figures are really in support of attempting immunization during the incubation period.

‡ All children who were exposed to infection within one month of the first dose of vaccine have been excluded from this table.

When failures of immunization are reported in vaccinated children it should be remembered that there are many spasmodic coughs simulating whooping-cough,

and there should be bacteriological control in a suspected case. A correct clinical diagnosis of whooping-cough is important, but frequently this is lacking. All the reports of past experiments show the necessity for a reliable bacteriological guide to control the diagnosis, and this can only be found in the cough plate method. In a recent epidemic in 1937 I found that the cough plate gave a positive method of diagnosis in approximately 90% of cases during the catarrhal stage, and the first week of the disease. Thereafter the percentage of positive cultures dropped steadily until in the third week not more than 50% were positive. It requires some practice to become proficient in this method of diagnosis, but with care, any bacteriologist can become efficient in from two to three months.

In the western districts of London a year has elapsed since notification was made compulsory, and the opportunity was afforded of correlating the clinical diagnosis of the general practitioners, welfare centres, schools and general hospitals, with bacteriological diagnosis by the cough plate method. This revealed that more than half of the cases notified as cases of whooping-cough and referred to the clinic were not infected by *H. pertussis*.

In addition to its diagnostic value, the cough plate has given us confirmation of Leslie and Gardner's work on the phases of *H. pertussis*, and has drawn our attention to what may be a new disease, namely, parapertussis.

The Function of the Clinic

When in 1934 I first became responsible for preparing pertussis vaccine on a large scale, I found it necessary to start a diagnostic clinic, in order to ensure a constant supply of fresh strains. This clinic was soon extended to embrace treatment, and later prophylaxis, of the disease. The inoculation of the brothers and sisters of our patients, as well as some of those who had been in contact with them, either at school or at the welfare centre, provided us with a ready means of testing the potency of our vaccine. Most of the inoculations, therefore, took place during the incubation period and during constant exposure, and this was a very severe test for the vaccine. Although prevention was apparently secured in only about 25% of child contacts, we were able to modify the severity of the disease in perhaps another 50%. These results agree with those of Madsen in 1929 (Table II), who attempted immunization during a fierce epidemic in the Faroe Islands. Since by our system of dosage it was impossible for the inoculated children who contracted the disease within one month from the commencement of the course to have acquired immunity, I have not included this group in my records.

The Choice of Antigen

Generally speaking, no chemically altered vaccine is as good as the simple suspensions of killed bacteria, and pertussis vaccine is no exception. A simple suspension of killed Phase I strains is the only antigen which has so far proved of value in recent field experiments.

However, such a huge dosage has been demanded by most clinicians that a constant search has been made for something better, and many attempts have been made to modify the vaccine.

It has been argued that if the antigens were in solution they must be more effective, and attempts were made to find a soluble pertussis antigen which would be more quickly assimilated into the body. Phase I strains of *H. pertussis* elaborate a toxic substance which is not a true exotoxin in that it is not antigenic. This toxic substance, and most other chemical extracts or fractions of the organism, are

unstable and easily destroyed during their preparation, and so are incapable of producing a solid immunity. This, of course, does not apply to the F.68 fraction of Cruickshanks and Freeman (1937) which was apparently fully antigenic, and very stable in the dry form. Undenatured bacterial antigen, Krueger (1933), at first had a very great following, but it has been shown by Lawson experimentally, and by Singer-Brooks clinically, to have no value as a prophylactic.

TABLE III (AFTER SINGER-BROOKS).—COMPARISON OF UNDENATURED BACTERIAL ANTIGEN AND PERTUSSIS VACCINE FOR PROPHYLAXIS.

Antigen	No. inoculated	Exposures	Attacks	%
U.B.A.	95	34	28	82
Controls	77	23	19	83
Vaccine (80,000 million) ..	272	42	5	12
Controls	256	71	62	87

For Lawson's figures *see* Table I.

It will be recalled that the antigens in diphtheria toxoid, originally prepared in solution, are now deliberately precipitated by alum to make them more effective. Harrison, Franklin and Bell (1938) have reported favourably on the use of alum-precipitated pertussis vaccine. Following the suggestion of Ledingham (1939), we combined pertussis vaccine with alum-precipitated diphtheria toxoid, and found that in this combination the vaccine contained a good antigen, and stimulated the production of both agglutinins and protective substances in mice.

The Dosage of Pertussis Vaccine for Maximum Immunity

The optimal dose of pertussis vaccine for prophylaxis has not yet been settled. In America, the common dosage given in a course of from two to four weeks is 80,000 million organisms. Sauer started with a dose of 22,000 million bacteria, but rapidly increased it to 80,000 million. So impressive are his results that all other American workers appear to have followed him, and strictly adhered to his course of immunization. Kendrick and Eldering (1939), in the biggest and best field experiment yet recorded, chose a dose of 70,000 million bacteria. Silverthorne, in Canada, has given up to 120,000 millions. I cannot believe that a dose of 120,000 millions is necessary for the immunization of a child under 1 year of age. The vaccine is not at fault; it is the method of application, in relation to the induction of immunity, which has not received due consideration.

Since individuals differ enormously in their powers to immunize themselves, there is no prophylactic method of immunization which can guarantee protection in all cases. In young children especially, it is desirable to choose doses of vaccines producing a good immunizing response without unreasonable discomfort to the patient. Various doses will give good protection, but the mere quantitative increase of any dose will not substantially raise the percentage of children protected.

Sauer states that immunity takes from two to three months to develop. This is a great handicap during an epidemic. Such large doses as are recommended by Sauer put too heavy a strain on the process of immunization in the young child, and immunity is delayed. In prophylactic inoculation the primary dose need not be more than that amount necessary to initiate the child's immunizing mechanism, and prepare it to respond quickly to a later stimulus, either the actual infection or another dose of vaccine. When response to the primary dose has been shown by the production of antibodies, the process of immunizing can then be carried further. Park

(1936) has shown the effect of different doses from 1,000 million up to 88,000 million, and these are given in a modified table (Table IV). An attack rate of only 3% was obtained with doses of 1 to 15,000 million, but an attack rate of 1% was still shown when doses of 66 to 88,000 million were given. Kendrick (1939) also mentions that a small number of children who had received only 4 c.c. of vaccine had an incidence of 2·8 per 100 person years, while those who received the whole course of 7 c.c. had an incidence of 2·3. These figures confirm our statement that there is not sufficient evidence in favour of the very large dose.

Effective prophylaxis consists in a primary stimulus followed by a secondary stimulus after an appropriate interval. In antityphoid vaccination, which has proved very effective, the interval between the first and second doses is only ten days, but with antigens such as diphtheria toxoid or tetanus toxoid the most effective interval between the primary and secondary stimulus is one month or longer. Toxoids are slow immunizers. Similarly, pertussis vaccine is a slow immunizer, and doses must not be given too close to one another. It is far better to allow an interval of one month before continuing with stimulating doses. The system adopted in America of increasing the dose after every clinical failure may be of questionable value.

TABLE IV (AFTER PARK).—PERTUSSIS PROPHYLACTIC VACCINATION.

Total dosage (× 1,000 M.)	Children on each dose	Developed pertussis from 1 to 18 months after vaccination	Incidence 1 to 18 months after vaccination %
65–88	793	6	1
50–60	604	10	2
30–49	666	8	1
16–29	222	5	2
1–15	422	13	3
		Controls	
Total number	6,031	391	7

With this in view, I have for the last four years at our Clinic at St. Mary's Hospital used the following scheme of dosage :—

Dose 1 : 4,000 million with an interval of three to seven days.
Dose 2 : 4,000 million with an interval of three to seven days.
Dose 3 : 4,000 million with an interval of at least one month.
Dose 4 : 4,000 million.

In a test group of 513 children with 46 known and 45 suspected exposures not a single case of whooping-cough occurred. In the control group of 154 children with 115 exposures, 89 cases of the disease developed.

The following case is a striking example of the value of the secondary stimulus even after a long interval.

A young adult who had never had pertussis was inoculated as follows :—

1937 : Five doses each of 4,000 million in the course of twenty-eight days. Maximum titre of agglutination, 1 : 250.

1938 : One dose of 4,000 million.

1939 : One dose of 1,000 million. Agglutination titre after ten days 1 : 10,000.

After the first period of injections there is a fair response, but not comparable to that found after the stimulating dose two years later. With the rise in agglutinins there is also an increase in the protective substances in the serum, which has been demonstrated experimentally in mice. This method of giving a final dose after a

considerable interval to induce a satisfactory secondary response has not previously been used in pertussis prophylaxis.

This secondary response has also been noticed by Wu and Chu (1938), and Miller and Silverberg (1939); but they have not employed this method deliberately in the immunizing process. Most of our immunization had to be carried out when our patients were exposed to infection; time, therefore, was always an important factor, and the month gained by our course was important.

The American workers, however, commenced immunization at a fixed age in welfare centres. Our system at St. Mary's Hospital provides for smaller doses which please both parent and child, and this demonstrates that if an inoculated child is exposed to infection there is plenty of time to call forth a secondary response of immunity during the incubation period.

In reviewing the results of prophylactic inoculation for pertussis we find that if immunity breaks down at all, this usually occurs during the second year of life, when the child starts to mix with others, and so greatly increases the chance of picking up infection. If, however, another suitable inoculation can be given at this period, immunity is at once stimulated and often rises far higher than at any time during the first course of immunization. Moreover, if a child who has been so "prepared" by inoculation to respond rapidly is exposed to infection at some period there is plenty of time during the incubation period to call forth a response to a fresh dose of vaccine. From Table II it will be seen that in a large proportion of exposures the infection itself is sufficient to stimulate a sufficient response in the "prepared" child to save it from an attack of whooping-cough. However, when it is essential to avoid an attack of the disease, no harm, but possibly much good, will result from giving a stimulating dose of 4,000 million pertussis vaccine.

Age and Immunization

Children born into a household where there is a case of whooping-cough are liable to contract the disease during the first month of life. The youngest case of typical whooping-cough that occurred within the scope of the clinic was 3 weeks old. Newborn children have been immunized by vaccines, but it should not be lightly undertaken. Madsen (1933) has reported two cases of death following inoculation with pertussis vaccine in newborn children. Our experience is that the best method of prevention in very young children is to isolate them from the infected members of the household by placing them under a muslin covering, and if exposure is known to have taken place, to attempt passive immunization by the use of convalescent serum. By adopting these measures several children born under these circumstances have been protected from the disease.

The immunization of children under 6 months of age against any disease, except perhaps against vaccinia, is difficult to attain. The response to pertussis vaccine is usually slow and incomplete, and our experience has shown that the earliest age at which immunization can be successfully attempted is between 6 and 12 months. Children of this age may safely be given the full scale of dosage, and from this period until 7 or 8 years of age they respond well, and are easily immunized. To save repeated inoculations young children may be simultaneously immunized against whooping-cough and diphtheria. The response to both antigens is equally good, and at least as good as when each antigen is given separately. In these children the reactions to pertussis vaccine are negligible and can be ignored.

The only contra-indications to the immunization of very young children are debility caused by other diseases, or malnutrition. Children immunized in late childhood make a good immunity response, but the reaction to the vaccine in this

group is much more marked, and often delays the immunization course. In the few adults who have been given a full course of pertussis vaccine the reactions were generally severe and painful.

Immunization may safely be undertaken during epidemic periods, though, of course, this is not the best time to choose. Madsen prefers to wait until an epidemic starts before carrying out universal inoculation but he is practically alone in advising this procedure.

Duration of Immunity

Immunity in whooping-cough, both naturally and artificially acquired, is generally considered to be lifelong, but there are cases of apparently genuine second attacks. These second attacks occur where the exposure is intimate and prolonged, as in families, orphanages, and other institutions, where there also is a large percentage of non-immune individuals. Seigel and Goldberger (1937) have demonstrated that many mild and atypical cases of whooping-cough have occurred in these circumstances in children with a previous history of the disease. They reported that the incidence and severity of whooping-cough were the same in those who had had previous attacks as in the inoculated children when exposed to the disease. It is not surprising, therefore, that artificially acquired immunity as produced by vaccine also broke down. However, in both these groups the disease was much milder than that seen in the control non-immune groups. Thus, in the face of exaggerated exposure, immunity can only be relative.

Prophylactic immunity may be expected to protect over 90% of the children inoculated, and from the point of view of the Public Health authority this will be satisfactory. The general practitioner will also find prophylactic immunization worth while, but in his own interest and that of the child, he will find it advisable to be prepared to give a further dose of vaccine if the child is exposed to infection. The long incubation period of the disease allows the child to reinforce his immunity after the additional dose of vaccine and so prevent an infection.

SUMMARY

The best age to start immunization is during the first or second years of the child's life.

Among the inoculated children the attack rate is less than 5%, and the communicability rate is less than 10% as against 60–90% in the control groups.

The primary immunizing dose of vaccine need only be sufficient to establish a sound basal immunity. Once this basal immunity has been established the immunity can easily be stimulated by subsequent doses of vaccine, which act in the nature of a " secondary response ".

By using this " secondary response " and a total dosage of only 16,000 million organisms, apparently good immunity was attained. In a test group of 513 children with 46 known exposures and 45 suspected exposures not a single case of whooping-cough occurred. In a control group of 154 exposures 89 cases of the disease occurred.

An additional dose of 4,000 million organisms should be given subsequent to the immunization course, when the child is known to have been exposed to the infection, or starts school life.

If the disease occurs in a vaccinated child it is usually mild or atypical.

The only reliable vaccine is one made from a suspension of killed Phase I strains of *H. pertussis*.

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Section of Neurology

President—GEOFFREY JEFFERSON, M.S.

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Extrasellar Extensions of Pituitary Adenomas

PRESIDENT'S ADDRESS

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THE extensions of the pituitary adenomas beyond their average confines require definition. Although everyone knows roughly what is meant by the term, no description exists. Harvey Cushing illustrated one or two, in parentheses, in the text of papers describing the symptoms and the surgery of pituitary tumours, and Henderson (1939), in a detailed review of Cushing's cases, devoted a small section of his paper to them. Examples will be found scattered through the literature of the earlier writers, but since attention became focused on the surgical treatment of the "strumous adenomas" interest has been centred on the smaller types which give the best operative results. The influence of this happening on our conception of the adenomas will be discussed, and indeed this paper has the double purpose of calling attention to the less typical cases, and of suggesting that we do not know the story of the pituitary unless we include these others in our survey. That point does not seem, hitherto, to have been appreciated as fully as it deserves. Cushing himself was always most interested in the cases which gave the best results, and in his time it was proper that the emphasis should have been laid on that note. Other writers have, quite naturally, followed his lead. But to do so leaves the history but half told.

Every enlargement of the pituitary results in an encroachment on neighbouring tissues. One might correctly speak of extension as taking place in all directions, downwards into the sphenoidal air sinus, outwards towards or into the cavernous sinuses, upwards into the cranial chamber and then by further proliferation either in front of the chiasma into the anterior fossa, behind it into the 3rd ventricle and hypothalamus, or below it laterally into the middle fossa. In its most exaggerated form it is a fact that such extensions take place in several directions at once, and tumour tissue may find its way even into the posterior fossa, as will be illustrated later. It appears then that extension must be a name given to any exceptionally florid adenoma, which, once its restraining bonds are broken, might build a prodigious tumour were it not for the predecease of the patient. Such as retain a globular form (and some do so) I should prefer to call "massive" adenomas, reserving the term extension for those which take an hour-glass or irregular shape in which the extrasellar portion is at least as large, and almost always larger, than the intrasellar portion.

The most extensive adenomas are the malignant, those which burst their capsules and not only form an intracranial mass but also invade the cavernous sinuses. In order to curtail the present paper a full description of this important group must give place to a shorthand note, leaving them for another occasion. Great size alone is not a sign of malignancy. Theoretically it might be assumed that gradation from small to great would be the natural procedure of all adenomas. It is, in part, the thesis of this paper that this assumption is no less incorrect than that they are all the same, with a completely standardized clinical picture.

That intracranial extension must cause important variations in the clinical picture is self-evident ; they may indeed alter it until it is almost unrecognizable. What is more, the growth qualities of the tumour and its mass have a considerable bearing on prognosis, taking the long view, and on operative mortality. It is only the smaller tumours, chiefly intrasellar, which can be operated upon with the margin of safety which we desire. Considerations of this kind lead one to the description of an ordinary pituitary tumour, one that has no special characteristic attributable to its size and ramifications.

The Average Pituitary Tumour

The steps by which the various pituitary adenomas came to be recognized are well known: the publication on Christmas Eve of the year 1900 by Benda of his discovery of acidophile granules in three tumours from acromegalic patients, the designation of " chromophobe struma " to describe the neutrophil adenomas (Cushing, 1912) causing hypopituitarism and the description by the same author in 1932 of the basophilic syndrome in an inclusive statement.[1]

The importance of these discoveries has been that each type of adenoma has slowly had attached to it a typical syndrome. In the formation of these symptom-sign complexes, history shows a repetition of a certain train of events which does not vary in its plan, whatever the disease. After the preliminary state of complete ignorance comes one of puzzled awareness until an individual, by intuition, crystallizes a disease pattern out of an amorphous group of cases. After tentative acceptance comes a period of conflicting evidence, and of apparent inconsistencies, which in the end are found to be no longer antagonistic if the original plan is slightly modified. Next follows the period of codification and clarification. The simple facts are seized upon, the greatest common measure of similarity applicable to all cases is sought out, and a standardized picture formed, clear enough to be memorized. Such formulation has the advantage that it can be taught to students in a clear way and, with greater difficulty, grafted on to the knowledge of those already practising their art. These didactic pictures are drawn, as I have said, from the average of symptoms and signs, shorn of variants which might blur the clarity of the outline. But formulation, however praiseworthy its intention, and however useful its practical benefits, has certain dangers. We may come to believe that the simple picture represents the whole of something which is, in reality, very complex. We are unaware, or only vaguely conscious, that the typical case is a high abstraction of our minds. No little

[1] My own interpretation of the various events is this : Cushing did not of course discover the chromophobe cell or even the adenoma. It was Flesch (1884) who first observed chromophils and Hauptzellen chromophobes. Schoenemann (1892) first called the former " eosinophils ", Benda (1900) preferred the name " acidophils ". It was Benda (1900) who first recognized the association of acidophil tumours with acromegaly, and Loewenstein (1907) who studied, in Ribberts' laboratory, the first chance findings of small chromophobe adenomas in a post-mortem study of pituitary glands from patients dead of disease elsewhere. The basophil cell was recognized first by Schoenemann (" zyanophil " 1892), and Erdheim first distinguished histologically a basophil adenoma (1917), having already (1903) suggested that anlage tumours and cysts were derived from Rathke's pouch. Cushing's Pituitary Body (1912) brought all the previous work on the adenomas to a focal point, presenting a series of clinical cases with chromophobe and acidophil tumours, the diagnosis having usually been established by biopsy during life. He compared their signs with those resulting from animal experiment. He found a parallel between the loss of pituitary function that accompanies the chromophobe adenoma and that following hypophysectomy in the dog. I have therefore given the chief credit to Cushing for the chromophobe picture because no one before 1912 had seen the problem so clearly or had had so much experience. Erdheim's basophil adenomas were probably cell aggregates ; he could not correlate them clearly with any clinical state. We have yet much to learn about " basophilism ". All the previous work on pituitary cytology has been superseded by the work of Severinghaus (1932–38) and Rasmussen (1933). Severinghaus has rebutted Benda's evidence of the existence of a fourth cell, containing mixed acidophil and basophil granules (Benda's " amphophils ", 1900).

of the thrill, which most of us have experienced, in encountering a typical or textbook case arises from its being a rare experience.[2]

This is true of most diseases; in neurology the symptomatology of disseminated sclerosis and of cerebellar tumours comes to mind, but it is difficult to know what to exclude in any speciality.

The pituitary syndromes began with a heavy endocrinal emphasis, but attention has become more and more sharply focused on the ocular manifestations, and especially on the visual field disturbances, with the radiological picture important, but not dominant. This change marks the growing importance of the surgical therapeusis of pituitary adenomas.[3] Standardization of the clinical results of the lesion tends to make us regard all pituitary tumours as being standardized in shape and size—perhaps something the size of a walnut. We know that the operative results are, in the main, excellent and we are puzzled, and indeed rather hurt, if a case behaves in a manner outside its scheduled pattern. We might further come to regard the type of case with which this paper deals as a curiosity, as the corner of a corner in medicine. In this we should be wrong, for these cases with extrasellar extensions give us part of the life-history of the pituitary adenoma and we know but little of the latter if we do not know of extrasellar extensions as well.

Cause of Extrasellar Extensions

In the main there are three factors in the production of extrasellar extensions. They are (*a*) the growth urge of the adenoma, (*b*) the state of fixation of the chiasma, and (*c*) the shape of the pituitary fossa and the nature of its diaphragm. Each of these requires a few words of explanation.

(*a*) *The nature of the adenoma and its growth tendency.*—Undoubtedly the most important factor must be the innate urge of the adenoma to enlarge progressively or intermittently. We know that the tendency to enlargement is by no means uniform. In the "benign" type of acromegaly, known in Marie's time, an adenoma with toxic qualities produces skeletal and somatic alterations, then ceases to grow. Such an acromegalic may live a long life without evidences either of continued pituitary toxicity or of encroachment of the adenoma on neighbouring structures. This behaviour causes no surprise, for we are familiar with similar adenomatous masses in another endocrine gland, the thyroid, where an adenoma reaches a certain size and, with minor fluctuations, remains not only the same for decades but never at any time occasions any symptoms. It seems probable that the pituitary and thyroid adenomas are similar in their nature and in their origin.[4] The original title of "pituitary struma" was not entirely wrong, in that it suggests the pathogenesis of the lesion. In adenomas the tissue anarchy is a local one within the gland, and we suppose that all its other cells have at one time proliferated excessively,

[2] Much of the difficulty which the young doctor finds in his first contacts with the sick after qualification arises from the fact that he has been educated on theoretically typical cases. He is baffled by the variants which actually form the greater mass. The student prefers his teachers to be dogmatic and, as it turns out, tellers of but part of the truth.

[3] The implication that endocrinal changes are unimportant is not intended. Not only are they important to the sufferer but their study has led to great enrichment of physiological knowledge. It is in practical daily usage that they have proved confusing, as is illustrated by the reluctance of the ophthalmologist to make a diagnosis of pituitary tumour when endocrine changes are absent. This has been a handicap not so much to neurology as to the patients themselves; fortunately a great advance can be made by the insistence that we should use as the title of our preliminary diagnosis "chiasmal lesion" and fill in the details of its causation only after full study. Confusion has arisen from the attempt to carry the diagnosis through to a conclusion on hasty examination and incomplete evidence; the consequence has too often been either no diagnosis at all or a wrong one.

[4] The endocrinal inter-relationship of the pituitary and thyroid glands is established by both clinical and experimental evidence, and there is little reason to suppose that their activations are based on dissimilar principles.

though the majority have regressed. The pituitary is so small that an adenoma crushes its cells out of existence (though sometimes they may continue to function) and then what they have to tell, what traces of change they might show, is undiscoverable. Once established, the adenomas behave like tumours in their tendency to continue growing, although we can find no sign of continuous compulsion in the state of the body metabolism. The urge, therefore, appears to be intrinsic. Another, and different, comparison can be made between the adenomas of the two glands, their tendency to be solid, or to have diffluent, or again, cystic, contents. The diffluent pituitary adenoma is fortunately common and rarely large. It is the solid adenoma with a strongly marked fibrous stroma which at once builds the largest tumour and at the same time makes them most difficult of removal. We shall return

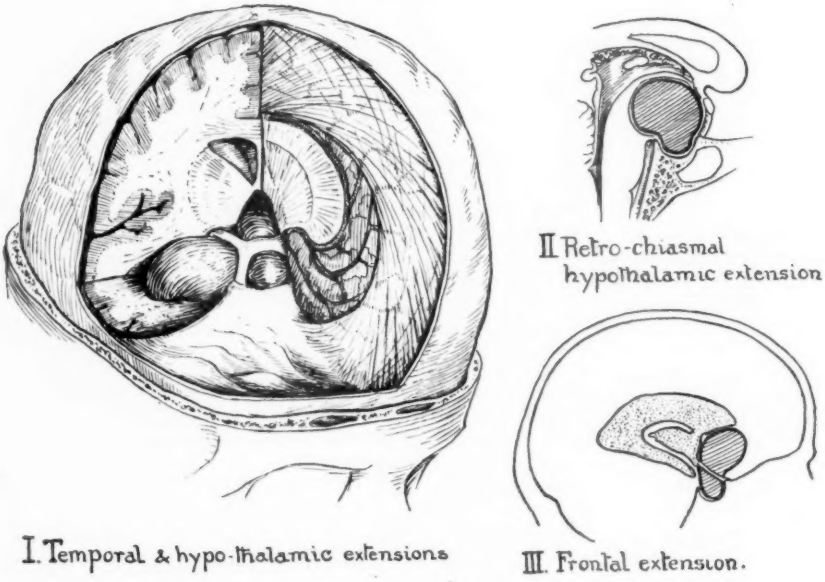


FIG. 1.—Diagram of pituitary extensions.

to the question of growth tendency when we come to discuss the so-called " malignant adenomas ". These reflections on the intrinsic growth urge of the adenoma may conclude with reference to Cushing's series (*see* Henderson, 1939). For whereas some of the cases survived for twenty years after operation, and over half the cases were well for long periods, others died relatively soon. Although it is comforting to the surgeon to believe that operation has greatly prolonged his patient's life, one must admit that the proliferative abilities of the tumour must always be the deciding factor in a situation where all of it cannot be completely extirpated.[5]

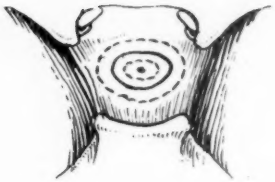
A distinction is made here between improvement of vision as a result of opera-

[5] My own experience and my own results are similar to Cushing's and give the impression that the rare pure cyst and the commoner diffluent adenomas sometimes allow of almost complete removal. But even in the most favourable example a few cells are left behind, and, if these have the necessary intra-cellular progressive energy, they can cause early recurrence with eventual death.

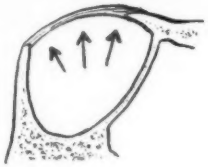
tion and long-range survival. It cannot be denied that operation must often retard the growth of a tumour (whether X-ray therapy helps we do not know with any certainty; Cushing's figures prove that it is helpful, though why it should be more so after operation than before is not clear). However this may be, an examination of the cases which follow deepens the impression that the most important single factor in the construction of large extensions of adenomatous tissue outside the sella is the vital urge of the cellular structure.

(*b*) *The fixation of the chiasma.*—There are objections, at first thought, in accepting the condition that fixation of the chiasma can have any influence on the size of a pituitary adenoma, for the chiasma is a structure which has, it is true, a not unimportant tensile strength, but not sufficient to restrain the growth of a tumour. When the chiasma is normally fixed an adenoma must make firm contact with it after it has risen 2·0 cm. above the level of the sellar diaphragm, and must then begin to cause some disturbance of vision (though, maybe, so slight a change as to pass unnoticed for a time). But if the chiasma is abnormally fixed the adenoma may grow for long before it seriously disturbs sight. Case 3 is an example of an adenoma being present for twenty years before it was finally operated upon, and in another (Case 9) it had presumably been present for twenty-four years. Both patients had, eventually, large but slowly growing adenomas; the only reason why the tumour had not caused symptoms before was because the chiasma was abnormally fixed (in one case post-, in the other pre-fixed). This is the explanation of the interesting series of cases of chiasmal lesion without optic atrophy reported by McConnell and Mooney (1938); the tumour does not make direct pressure on the optic nerves. Cushing (1933) hinted at the probability that central scotomata probably meant a retro-chiasmal extension (since the macular fibres appear to decussate in the posterior part of the chiasma) and Henderson (1939) in a further survey of Cushing's cases, supported the view, which is undoubtedly correct. I would go further and say that the tumour is always likely to be large when bilateral central scotomas are present. Although pre- and post-fixation of the chiasma are roughly equally frequent (4 and 5% respectively in Schaeffer's observations, as given by de Schweinitz) the surgeon is made more acutely conscious of pre-fixation, because it interferes so disastrously with his exposure of the tumour. But whichever the variant is, its tendency must be to allow of the unnoticed enlargement of the tumour. It is for these reasons that bilateral scotomatous fields suggest pre-fixation, and that fact again suggests that the tumour will be large. There is another possibility of scotoma formation, especially when unilateral, always to be borne in mind, that there may be a localized herniation of adenomatous tissue through the capsule impinging either on the chiasma or on one optic nerve. Such a happening may cause not only a scotoma but a monocular partial superior altitudinal hemianopia. Examples will be seen in the gross specimens illustrated in figs. 6 and 11. The significance of these tumour herniations will be discussed later.

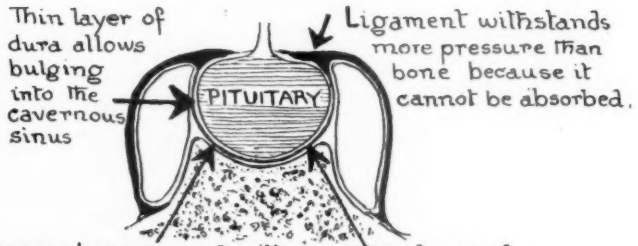
(*c*) *The sella and sellar diaphragm.*—Fig. 2 shows in diagrammatic form the alterations in the sella produced by pituitary adenomas and the influence of the sellar diaphragm in restraining extrusion. Little comment is necessary to amplify what the schema shows. The diaphragma sellæ is a thin fibrous sheet at its centre, where the pituitary stalk emerges through an opening which varies greatly in size. Sometimes nearly 1·0 cm. of the dorsal surface of the gland can be seen through the opening. At the sides it is thickened by the interclinoid ligaments which contribute to the strength of the diaphragma, fading in a mesial direction. But just as it is possible to hold down a tennis ball by two fingers widely separated, so these ligaments rather than the diaphragma take the chief thrust of the tumour, which balloons out sideways under them towards the cavernous sinuses on either side. Ligamentous tissue is not easily, if at all, destroyed by benign tumours (certainly not by plain pressure)

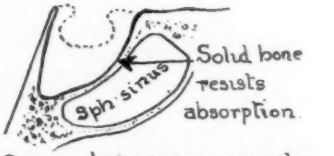


Variations in size of stalk opening in sellar diaphragm



Elevation of anterior clinoids by pull of ligaments


Thin layer of dura allows bulging into the cavernous sinus
PITUITARY
Ligament withstands more pressure than bone because it cannot be absorbed.
Spongy bone covered with very thin layer of dura is easily absorbed.



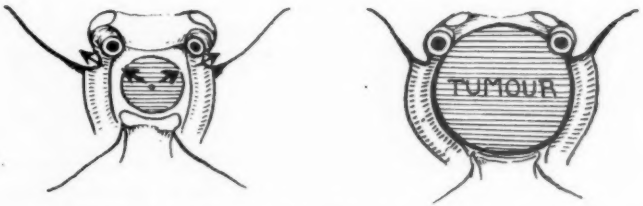


FIG. 2.—Mechanism of sellar alterations.
(E. W. Twining.)

and bone, unexpectedly, proves to be much more malleable. As for the bone itself the cancellous (and thicker) variety proves to be physiologically less resistant than the compact kind, so that the tumour enlarges more easily downwards and backwards towards the basi-sphenoid than forwards into the sphenoidal air-sinus. Thus arises the eccentric V-shape sella, characteristic of the pituitary adenoma. In fig. 12 for example the thin compact bone roofing the sphenoidal air-sinus has proved itself remarkably resistant to depression by the large overlying tumour.

In those cases where the sella is saucer-shaped and shallow a suprasellar extension is the natural result, though its size chiefly depends, at the time seen, on the other two factors just discussed (especially the first). The lateral walls of the sella, and the breaking through of adenomatous tissue into the cavernous sinus, will be described in its proper place. A last word must be added on " sharpening " of the anterior clinoid processes. The figure shows the late E. W. Twining's explanation: that the tumour presses the internal carotids against these bones and wears them away by the water-hammer of the pulse, and not by the direct pressure of the adenoma itself. That observer's figure of the elevation of the clinoids by the drag of the interclinoid ligaments is also illustrated.

We may now pass to the discussion of the various extensions. It will be realized that they are all examples, and only variants, of the same thing but although their classification is, in a wide philosophical sense, quite artificial, there is good clinical reason for grouping them because their symptoms and their signs differ. Fig. 1 shows schematically some of the various intracranial extensions which may be classified as—Hypothalamic, Frontal, Temporal, Pharyngeal, and Posterior fossa protrusions.[6]

It was mentioned earlier that a distinction should be made between mere massiveness in a tumour and extension proper. I regard a " massive " tumour as one which is merely a very large tumour, the diameters of which are equal.

Hypothalamic Extension

Most of the more massive tumours in the series have extended towards the hypothalamus, usually behind a prefixed chiasma. In this series there is one excellent example of an hour-glass extension, which is, on the contrary, so frequent in the pituitary anlage series. There have been several of that nature in this material (e.g. Cases 9 and 11).

The outstanding features of these extensions are headache and somnolence, thirst, polyuria, temperature variations; alterations in cardiac and respiratory rhythm are less common. As a rule tumours which merely indent the hypothalamus without invading it do not produce outspoken hypothalamic disturbances, though this is not an invariable rule. Severe headache is rare in chromophobe adenomas and should always raise the suspicion that an extension is present. Neither headache nor hypersomnia are sure indications of the direction of the extension, but since a hypothalamic extension, of all others, is most likely to produce internal hydrocephalus the severest headache should occur in this type.

Case 1.—*Chromophobe pituitary adenoma. Amenorrhœa.*

Right homonymous hemianopia. Bilateral optic pallor. Very severe periodic headaches. Fugitive left abducens weakness. Operation. Death from hæmorrhage into a suprasellar extension invading the 3rd ventricle.

N. A., aged 32, was referred by my colleague, Dr. A. H. Holmes, with the diagnosis of pituitary adenoma, August 30, 1934. Two years ago menstruation ceased suddenly; she became irritable,

[6] Henderson classified Cushing's examples into frontal, temporal, Sylvian, and thalamic. I have seen no important Sylvian extension, though I have observed tumour tissue overlying an optic nerve, tissue that was drifting in a Sylvian direction. I doubt whether a true massive Sylvian variety exists as a solitary feature; perhaps once attention has been directed to it a rare example may be found. I prefer " hypothalamic " to " thalamic " as a name for upward and backward protrusion. The posterior fossa extensions, apart from protrusions via Meckel's cave, are newly designated.

chiefly because of violent headaches, usually in the left temporal fossa. She had gained considerably in weight. Recently she had become extremely lethargic and would lie in bed for hours. A week before admission her left eye had squinted inwards. On examination she was an obese woman with hypertrichosis; metabolic functions normal to tests; B.P. 125/85. There was a variable paresis of the left abducens; sometimes it was scarcely noticeable, and it was never seen to be complete, though she stated that it had been so for three or four days recently. The optic nerve heads were only faintly pale, but there was an incongruous right homonymous hemianopia of which she had been unaware. X-rays showed a moderate but definite enlargement of the sella. Cerebrospinal fluid pressure not recorded. Albumin 40 mgm.%. The pre-operative diagnosis was chromophobe pituitary adenoma with a left-sided suprasellar extension. It was assumed that her lethargy was due to endocrine disorders and her peculiarly severe headache to sellar distension. Operation was undertaken by an assistant and proved to be easy but, significantly, only after the right ventricle had been tapped; before that the brain was very tight. A large bluish adenoma was brought into view and easily evacuated with spoon and sucker. It was very

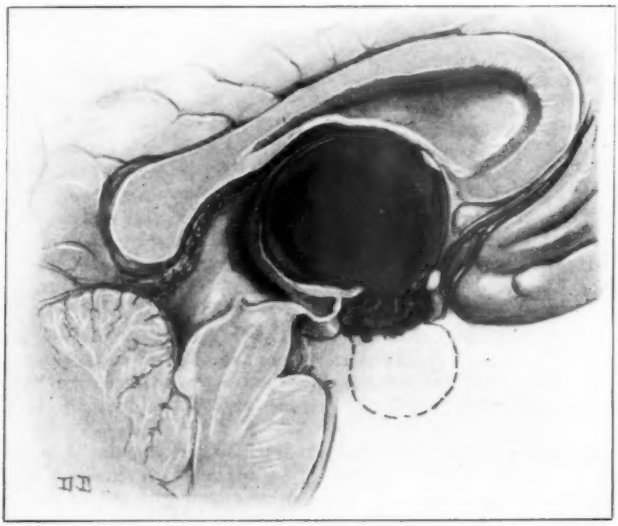


FIG. 3 (Case 1).—Hypothalamic extension of adenoma filled with blood.

vascular. Three hours after operation her temperature rose to 102° F. and in spite of antipyretic measures she died twelve hours after operation in a hyperpyrexial state. Necropsy revealed a large suprasellar extension full of clot filling the cavity of a suprasellar extension rising high into the 3rd ventricle (*see* fig. 3). The specimen resembles some of those of large basal aneurysms but histology supported the operation findings of chromophobe adenoma. The occurrence of violent headache in a patient with a chromophobe adenoma should have aroused greater suspicions, especially with the association of so uncommon a finding as homonymous hemianopia. A transsphenoidal approach could hardly have failed to excite a similar hæmorrhage, and one must write this down as a surgically irremovable lesion. There can be no doubt that the intraventricular cyst was a prefixed adenomatous extension and not a post-operative suprasellar clot which must have a different distribution.

Comment.—A similar death from hyperpyrexia within a few hours of evacuating a pituitary cyst, an operation that had proved very simple, remains unexplained from lack of post-mortem verification. But the very severe headaches that this patient also had suffered, and her entreaties for operation during a long period when she was undergoing X-ray therapy, make one suspect that she also may have had an identical and unrecognized upward extension behind the chiasma.

Frontal Extensions

A pituitary frontal extension (which has not previously been exactly specified) can be defined as a protrusion towards the anterior fossa, in which this protrusion is larger than the intrasellar portion. These extensions bury themselves in the surface of the frontal lobes or of one frontal lobe. Epilepsy is a common sequel, as it is with any frontal tumour. Three cases will be described.

Case 2.—*Huge suprasellar extension into the right frontal lobe.*

S. B. L., male, aged 54, an electrician, was admitted to the Neuro-Surgical Service of the Manchester Royal Infirmary, December 31, 1936, complaining of failing vision, severe headache,

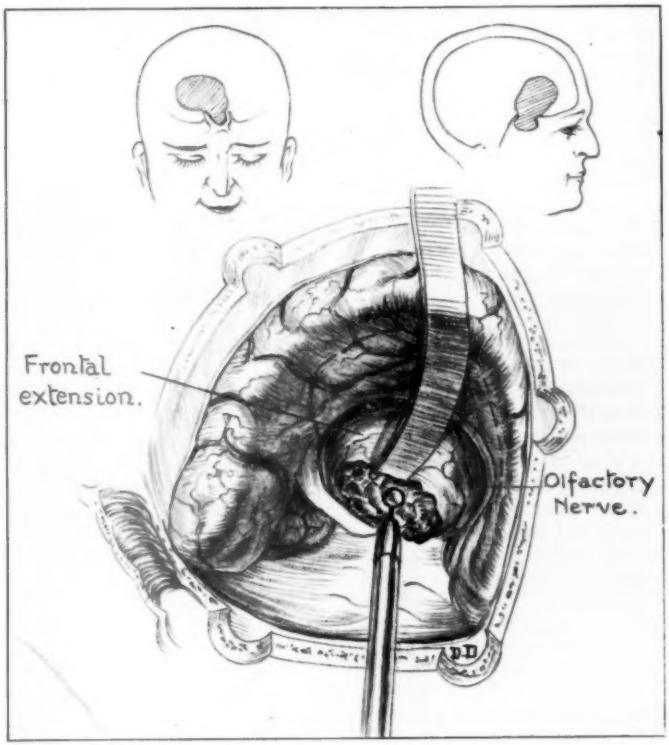


FIG. 4 (Case 2).—Sketch of tumour as seen at operation.

character changes; later fits. Eighteen months previously his sight had begun to deteriorate. Finally diplopia was a definite feature before the vision in the right eye became too bad for binocular vision. He was finally referred to Mr. G. F. Rowbotham, who diagnosed a pituitary tumour and transferred him to the Manchester Royal Infirmary. His wife had recognized personality changes—irritability, a distaste for company, and loss of ambition. By this time his sight had become so bad that he was having difficulty in getting about; he had not been able to read newspapers for four months. He became much worse after a severe generalized convulsion. His right eye, in which there had been a central scotoma, was now virtually blind, and he was suffering from continuous headaches often very severe. On examination there were

no neurological signs apart from vision. He was a well-looking man greatly worried by occipital headaches severe enough to make him dizzy. He had lost weight. There was no polyuria or hypersomnia. His memory was good, no behavioural peculiarities were observed ; no anosmia. The pupils measured 3·0 mm. and reacted to light. Ocular movements were normal. The optic nerve heads were very pale with the vessels rather small, no papilloedema. *Visual fields.*—Right eye : hand movements recognized in the nasal field only. Left eye : temporal hemianopia sparing macula. V.A.R. less than $\frac{6}{60}$; V.A.L. $\frac{6}{36}$. X-ray showed the sella a little enlarged, the floor depressed, more so on the left than on the right. The posterior clinoids were slightly eroded but the picture was not characteristic of the ordinary ballooned sella of the adenoma. Optic foramina not enlarged. B.M.R. + 5. Sugar tolerance curve shows slight retention ; fasting level 81 mgm.%. All other laboratory tests negative except the cerebrospinal fluid. Pressure low (80 mm.), proteins 100 mgm.%, globulin marked opalescence (Pandy). It was clear enough that this patient had a chiasmal lesion, but the unusual points were the sellar pattern, the severity of his headaches, his invalidism, and the generalized epileptic attack. The high cerebrospinal fluid protein might have indicated a meningioma, though there was no basal hyperostosis in the radiographs. An encephalogram showed the right ventricle pushed upwards and its floor indented as by a sub-frontal tumour.

At operation December 24, 1936, through a right Trotter flap an intradural approach was made to the lesion. The cortex was pale and the right frontal lobe voluminous and difficult to elevate. This difficulty proved to be due to the fact that a large mass of adenoma projected upwards into it from below. The right optic nerve was finally brought into view after dividing many adhesions. It was very thin and pale stretched around the base of a huge pituitary adenoma which rose to indent the frontal lobe. A full exposure of this large suprasellar extension was not possible. Its surface was smooth and dark red. After exposing a suitable area it was incised and a quantity of its soft contents sucked and punched away. Bleeding was free. The material removed was typical of a pituitary adenoma. Although the tumour was very greatly reduced in size it was not possible to evacuate it completely, nor to bring the chiasma into view. The operation was broken off and the wound closed with drainage. The patient made a smooth recovery. He returned to work in six months and three years later he was re-examined. He had had an occasional epileptic attack but was continuing his trade as an electrician.

Comment.—**The tumour in this case, although histologically a chromophobe adenoma, behaved like a frontal rather than a pituitary tumour. Its prechiasmal site led to the bitemporal hemianopia but its break through to the right frontal lobe gave him a central scotoma in the right eye and later made it blind. The severe headaches and character changes, the high protein count in the cerebrospinal fluid, all combined to suggest an extrasellar origin for the tumour.**

Case 3.—*Chromophobe pituitary adenoma.*

Seventeen years' amenorrhœa. Four years' history of generalized epileptic fits. Slight pallor of both optic discs. Normal fields. Massive suprasellar extension. Operation.

L. H., aged 37, was referred by Professor Henry Cohen. At age of 22 menstruation ceased suddenly, never to reappear. During the next twelve months she gained 3 st. in weight ; since then there had been a gradual increase to 12 st. but she felt reasonably well, finished her training as a nurse, and held posts as Sister. In 1934 she had an epileptic fit with no aura except a vague and brief feeling of dizziness. She had eight fits that day, but after one or two more during the next week they ceased. From that time on her history was one of occasional epileptic fits which usually ended the tenure of her official post. But she felt perfectly well as soon as the attacks were over. In 1936 encephalograms were made without any abnormality being discovered. In December 1938 Professor Cohen discovered that the pituitary fossa had been completely destroyed. This was difficult to account for, because there never had been, nor were there then, any symptoms or signs to suggest the presence of an intracranial tumour, save a relative hyposmia on the left. The optic nerve heads though pale showed a faint œdema, whilst the fields were full. She was admitted to the Neuro-Surgical Service of the Manchester Royal Infirmary in January 1939. She was an obese, slightly hypopituitary but generally normally active woman. B.P. 150/90. L.P. pressure 100 mm., albumin 55 mgm. Ventriculograms were made. Once again no unmistakable abnormality was discovered. There was no hydrocephalus, no ventricular displacement. Tomograms showed an unusually high 3rd ventricle with the

normal suprachiasmal and infundibular notches. The same technique showed destruction of the upper part of the basisphenoid with destruction of the dorsum sellæ and clinoids. A scooping out of the right parasellar region was also visible. The presumptive diagnosis was arrived at of benign chromophobe adenoma with upward and frontal extension. The high 3rd ventricle with normal inferior contour was not at that time given its correct valuation, which operation later showed an unusual degree of post-fixation of the chiasma. Operation was not at once undertaken because the patient's only disability arose from her epileptic incidents. It seemed uncertain that operation would cure them. However, a transfrontal exploration was carried out, October 29, 1939. There was now no trace of papillœdema, the discs were a trifle pale; the fields of vision showed a slight temporal upper quadrantic notch in the smallest isopters. A large hard fibrous adenoma was disclosed rising out of the sella, pre-chiasmally, and was seen to be indenting the inferior surfaces of both frontal lobes. The tumour proved to be too hard for radical removal, without first sacrificing the right frontal lobe. Only this step would have allowed of a sufficiently full exposure of the tumour to permit of a proper attack. But since the effect of such a step on her epilepsy was doubtful, nothing more than a partial removal was attempted. Recovery was uneventful, except that for the first few days she was a little disorientated, excitable, and complaining about minor annoyances.

Comment.—This is an admirable example of generalized fits occurring as the leading outspoken symptom of a pituitary adenoma. It is true that the amenorrhœa and obesity must be given pride of place in her history, but it was epilepsy that led to her seeking advice rather than amblyopia. A transient papillœdema was observed, hyposmia on the left, then slight pallor of the discs and a faint disturbance of her temporal visual fields. This adenoma was one of the fibrous, "rubbery", type so difficult to extirpate. It was lobulated and spread over the right optic nerve. Evidently it was a very slowly growing adenoma with no hint of malignant intention, and may continue to enlarge very slowly for years to come. After some twenty years (supposing it to have antedated the amenorrhœa by a year or two) it is even now no larger than a bantam's egg.

Another case of frontal extension illustrates an important practical point, the manner in which its presence makes exposure so difficult that amputation of a frontal lobe may be necessary to allow of proper visualization of the lesion.

Case 4.—*Chromophobe adenoma.*

Bitemporal hemianopia and failing vision. Lethargy. Excision of right frontal lobe to obtain exposure.

L. P., female, aged 27, was referred by Dr. Horsfall of Leeds. The leading symptom in this case was headache, radiating to the right frontal region, headache which gradually became more and more disabling. Six months later she became conscious of a temporal field defect in her right eye and on admission she had no useful vision on that side, and a temporal hemianopia to the left. There was no anosmia. She occasionally had diplopia during the past two years. She had gained 2 st. in weight, she was very sleepy, no energy, and was not interested in things. She would rather stay at home when the rest of the family went out. She had to give up her work on account of headache rather than defective vision. She volunteered no information and her history had to be got from her by question and answer. Amenorrhœa had been present for two and a half years.

At operation on August 6, 1937, it proved to be impossible to elevate the right frontal lobe sufficiently to bring the tumour into view. This was thought to be due to mucous obstruction of the intratracheal tube and venous congestion, so the operation was suspended. Eight days later under local anæsthesia conditions were found to be no better. The right frontal lobe had to be removed and a not very large extension dealt with summarily, leaving a collapsed capsule Improvement in her mental state was immediate. Two days after operation she was writing letters home.

The importance of this case lies in its illustration of the reason for the difficulties which may arise in exposure. If they are so great that the tumour cannot be seen we may be sure that at least a massive tumour is present, and that there is more

probably an extension. The after-history of this case was that her acuity greatly increased after the lobectomy and that she seemed to her relatives to be much more intelligent than she had been. The reasons for improvement, even though important brain tissue has been sacrificed, were advanced by the writer in 1937. Apart from some glycosuria in 1939 she has remained well.

Temporal Extensions

Adenomatous tissue may escape laterally from the sella below the chiasma and proliferate in the middle fossa. Probably there is no other reason why it should do so except that there may be an unequal proliferative urge in one part of the tumour. In a case of Cushing's the temporal extension crossed the middle fossa and, having eroded the temporal squama, came to infiltrate the muscle. The patient remained well nine years later, showing that the adenoma was not malignant. The next case (5) was very puzzling because there were clear signs of a left temporal tumour and yet there was bilateral optic atrophy. The problem was not solved until necropsy. In Case 6 a more correct pre-operative diagnosis was made. A further example of temporal extension will be found amongst the malignant adenomas (Case 11).

Case 5.

Fits 2½ years. Failing vision 2 years. Weakness right arm and leg 1½ years. Headaches 1 year. Nocturnal incontinence 4 months. Operation. Chromophobe adenoma with left temporal extension.

A. S., male, aged 41, was admitted to the Manchester Royal Infirmary January 19, 1935, under Dr. T. H. Oliver, who made the diagnosis of cerebral tumour. He gave a history of generalized epileptic fits which had commenced two and a half years ago, at a time when he had considered himself to be in excellent health. He had six attacks the first day and for some time after might have eight or ten in one day though without loss of consciousness. The attacks always commenced with a foul taste in the mouth and a bad smell associated with a feeling of dizziness. He became accustomed to these attacks, would stand still for two or three minutes until they were over. He was able to continue with his work until a few months ago, when he gave it up for a different reason, failing eyesight and difficulty in walking. For a year past he had observed a very slowly increasing weakness of the right arm and leg. Two years ago vision in the left eye had begun to fail and since then very slowly worsened. He was aware, in the end, that not only could he not see well with the left eye, but that he could not see to the right-hand side with either eye. Two years ago he had diplopia for a time and it had occasionally troubled him since. For a year past he had had severe headache, lasting for an hour, on rising in the morning. The ache was in the left temporal region and had improved lately. For one year also he had difficulty in walking, first the right leg was the worse, later the left, but at the same time the right hand had become weak as well. For four months he had been apt to wet the bed during sleep and was worried and distressed on this account. Mentally he was said to have become different, liable to short periods of depression and emotional instability. For some time past he had been sexually apathetic. On account of these mental changes, incontinence, and optic atrophy, he was thought to be a neurosyphilitic until serological studies negatived this diagnosis. On examination the most important findings were: Bilateral optic atrophy with normal vessels and nothing to suggest œdema or consecutive atrophy. V.A.R. $\frac{6}{18}$, V.A.L. $\frac{6}{36}$. Visual fields, right homonymous hemianopia, fairly congruous in size and shape. No anosmia in either nostril. No oculomotor palsies in spite of the history of diplopia. Pupils reacted sluggishly to light. No trigeminal pain or anæsthesia. He had right-sided pyramidal signs including a positive Babinski reflex. In spite of his complaint of weakness in the left leg also, allegedly worse recently than the right, there were no signs of pyramidal tract involvement on that side. Nor were there any sensory disturbances, only the history of gustatory and olfactory auræ. Lumbar puncture: The cerebrospinal fluid was yellow, contained 200 mgm.% of albumin, and gave a positive reaction for globulin. Wassermann reaction negative in blood and cerebrospinal fluid.

Radiographs of the skull showed enlargement of the sella, the dorsum sellæ could not be seen. Unfortunately he had an unusually pneumatized temporal bone, basal zygomatic air cells, obscuring the sella. Ventriculography gave definite evidence of the presence of a left temporal tumour.

A diagnosis of left temporal fossa (probably sphenoidal wing) meningioma was made, but the bilateral optic atrophy without a trace of œdema remained unexplained, and some uneasiness was expressed as to the correctness of the diagnosis.

Operation.—Through a left fronto-temporal Trotter flap the left temporal lobe was exposed. After a short search a curiously lobulated and smooth-walled tumour was located in the anterior end of the middle cranial fossa. The tumour was " uncapped " by excising an oval piece of the temporal lobe, 6·0 × 4·0 cm. A good view of the tumour was thus obtained ; it was dark red in colour with thin-walled vessels running in the depressions of its irregular surface. On commencing to loop the tumour out with the endothermy small cystic spaces were come upon here and there which made the nature of the tumour even more difficult to recognize. Its relations precluded the possibility of its being a glioma. Owing to brisk hæmorrhage progress was slow, and after four hours all hope of the total removal of the tumour was abandoned, for it seemed to be firmly attached to the sella or cavernous sinus on the outer side of the chiasma ; the carotid

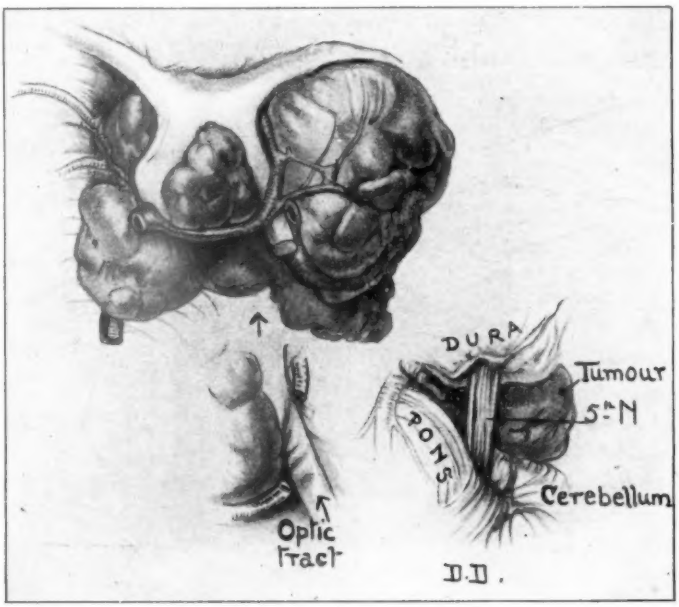


FIG. 5 (Case 5).—Drawing of lobulated chromophobe adenoma of pituitary.

artery was not to be seen. The whole of the floor of the temporal fossa was empty. Muscle grafts were placed over a bleeding point on the sheath of the Gasserian ganglion. The flap was replaced but the wound was reopened twenty-four hours later as he had not regained consciousness. The already weak right side was weaker still. No clot was found. The cause of the clinical state was acute cerebral œdema.

Post-mortem examination gave the answer to the various anomalies which had already introduced difficulties into the clinical and operation picture. The tumour was a pituitary adenoma which had entangled the visual apparatus bilaterally and had, apparently by chance, grown out under the optic chiasma to form the large tumour in the temporal fossa which had been removed two days before (*see* fig. 5).

The tumour was, of course, essentially inoperable. Even if the removal of the temporal extension had been successful, it seems unlikely that a second operation directed at the pituitary from the front would have achieved a really worth-while improvement in vision or length of life.

The tumour was mainly retro-chiasmal. Possibly a considerable amount could have been recovered if the left optic nerve had been sacrificed, but there was a formidable attachment of the carotid artery to the tumour.

A further example of temporal extension has recently (1940) come under the writer's care referred by Professor Henry Cohen.

Case 6.—J. D., male, aged 38, suddenly lost visual acuity eighteen months ago, so that he could not read, but after two weeks his vision returned. The left eye has been the worse ever since. Six months ago he began to experience sudden attacks of dizziness with a curious sensation creeping up the left side of his body, associated with a very curious smell that he could not identify (uncinate attacks). They lasted for a period of three months and then ceased. For one month he had had exceedingly severe right-sided headache of a paroxysmal nature and for three weeks he had vomited. On examination he was an obese man with depressed libido for many years. Bilateral optic atrophy, no anosmia. *Visual fields.*—Very incongruous. Left eye: Vision was lost except for a crescent which ran across the superior temporal and nasal quadrants. Macula vision was lost. Right eye: A clear-cut temporal hemianopia sparing the macula (fig. 6).

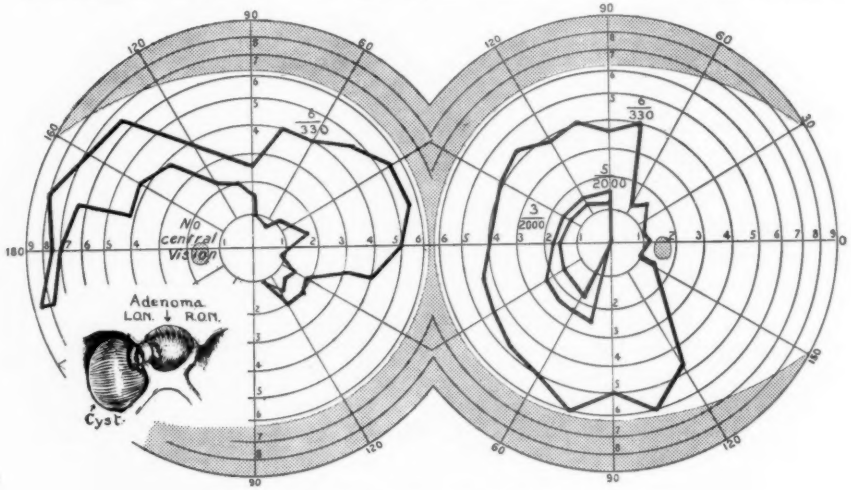


FIG. 6 (Case 6).—Visual fields.

Complete destruction of the sella turcica and of the left anterior clinoid. Cerebrospinal fluid protein 120 mgm., fluid xanthochromic at first puncture. No pyramidal signs. Subjectively a slight impairment of memory for proper names for a long time past. He was inclined to be somnolent. There was no sign of involvement of the nerves in the cavernous sinuses. This was evidently a massive pituitary adenoma with a left temporal extension. Ventriculography did not show the 3rd ventricle very clearly in the lateral view but in the antero-posterior the 3rd ventricle was shortened and pushed to the right.

A left osteoplastic flap was turned down which disclosed a rubbery asymmetrical pituitary adenoma under the left optic nerve, with a large cystic extension in the left temporal lobe. Recovery.

Protusion into the Cavernous Sinus

It must have struck all observers of pituitary tumours as curious that there are not more often signs of pressure on the cavernous sinuses and the nerves within them. There is something unexpected in the way in which a pituitary adenoma burrows into

the bone of the sellar bed and so rarely gives evidence of extending laterally where the boundaries are membranous. The fact is that the tumours do, actually, press heavily laterally, but that the structures there are sufficiently elastic to adapt themselves. Were it not so, oculomotor palsies and trigeminal anæsthesia would be as common a result of pituitary tumour as of cavernous aneurysm. In the latter the nerves are enclosed in the same sheath as the artery, and cannot escape. But there are often minor signs of involvement of the oculomotor fibres in the form of transient or persistent diplopia (e.g. Cases 7, 10); a frank paralysis of one or other nerve is rare. Trigeminal anæsthesia has, in my own series, been a definite sign that the adenoma has broken through into the cavernous sinus, and is important and grave evidence. Sensory changes in all three trigeminal divisions is a sign of invasion of Meckel's cave and perhaps of the sensory root (*see* Case 9). Although the nerves and vessels are never eroded by the tumour cells, a definite break-through into the cavernous sinus is, in my view, the certain criterion of malignancy. A prognostic distinction must be drawn, therefore, between the signs of protrusion of an encapsulated adenoma on the sinus, and those of actual invasion. An oculomotor palsy or paresis, as opposed to trigeminal anæsthesia, is not necessarily a bad sign. Case 7 illustrates this fact.

FIG. 7 (Case 7).—Chromophobe adenoma. Paralysis of right third nerve.

Case 7.—Chromophobe pituitary adenoma.

Bitemporal hemianopia. Right 3rd nerve palsy. Operation. Recovery of oculomotor paralysis.

E. N., female, married, aged 55, was admitted July 16, 1932, referred by Mr. Sumner of Preston. She complained of failure of vision and drooping of the right upper eyelid. Menstruation had ceased six years previously. For the last two years her eyesight had been failing, and three months ago the right eyelid had slowly closed after a short period of diplopia. She had had considerable headache, bitemporal and right frontal in distribution.

On examination she was a woman of medium build, right-sided ptosis being a striking feature (*see* fig. 7). There were no gross endocrinal disturbances except glycosuria which had been known to be present for the past three years and was accompanied by polyuria and polydipsia. She had bilateral optic pallor with a bitemporal field defect, scotomatous on the right side. There was complete paralysis of the right 3rd and 4th cranial nerves but not of the 6th. There was no anæsthesia in the distribution of trigeminus, the corneal reflexes being brisk. She had, however, suffered considerably from pain in the right forehead and cheek, with occasional neuralgic pains

in the right upper gum. This, together with the oculomotor paralysis, was suggestive of a saccular aneurysm of the right internal carotid artery in the cavernous sinus. There was no bruit. Radiographs of the skull showed considerable enlargement of the sella (2·7 cm. antero-posteriorly by 2·0 cm. deep); in addition the anterior clinoid processes were ill-defined and there were small areas of calcification below the level of the pituitary diaphragm. The sphenoidal fissure was not enlarged; it is apt to be so when an aneurysm rather than a pituitary tumour is present. Laboratory tests: Basal metabolic rate plus 8. High fasting blood-sugar, 117 mgm.%. Retention of sugar on oral administration of 50 grm. of glucose—260 mgm. after one hour, 246 mgm. at the end of the second. Urine loaded with sugar after two and a half hours. Ordinarily her urine contained sugar.

Comment.—Diagnosis was by no means easy. The glycosuria was more suggestive of a pituitary adenoma than of an aneurysm, but it might have been unrelated to her present condition. The bitemporal hemianopia indicated, as it always does, chiasmal compression without in any way certifying the nature of the lesion producing the visual disturbance. Pain in the forehead and teeth is much rarer with pituitary adenomas than with aneurysms. The one really certain point was the enlargement of the pituitary fossa, but here again there were flakes of calcification that might have been in the carotid wall. The precise nature of the tumour remained uncertain until the actual operation, when a large non-pulsatile swelling was seen between the optic nerves. On puncture with a needle clear yellow fluid was withdrawn demonstrating that she had a pituitary cyst. The capsule was incised and its contents rapidly evacuated by the sucker after some soft tissue had been punched out for microscopy. The tumour proved to be a cystic chromophobe adenoma.

Within three months of the operation the ptosis of the right lid and the oculomotor palsy in general had completely recovered. Eight years later she continues in good health with good vision, and without glycosuria.

The prolonged survival of this patient shows very clearly that the adenoma could have been in no way malignant. The most likely explanation of the oculomotor palsy is that there was a localized "nubbin" of tumour indenting the right cavernous sinus but without actual infiltration (i.e. that it was still encapsulated).

In a further case a similar recovery occurred, this time spontaneously, and the patient again remains well ten years later. In this patient the tumour must have very little intrinsic growth urge.

Case 8.—The writer was called to see a doctor, aged 25, who had during the night suddenly awakened with a severe pain in the head and had rapidly become stuporous. He had been in failing health for a year or more.

On examination he was seen to be a heavy-featured young man turning restlessly in bed in a darkened room. There was an oculomotor palsy on the right side. Lumbar puncture disclosed heavily blood-stained cerebrospinal fluid. No very detailed examination was possible.

A diagnosis of presumed aneurysmal subarachnoid hæmorrhage was made. He was not seen again for some months. In the meanwhile he had made a good spontaneous recovery and had been under the care of Dr. Gordon Holmes, who diagnosed acromegaly with hæmorrhage into the tumour breaking through into the cranial cavity.

Comment.—There is no doubt that this diagnosis was correct. X-rays taken later showed a gross enlargement of the sella turcica, and his features were those of an acromegalic, but not a very pronounced one. This was the first time that an important hæmorrhage into an adenoma had been seen, and it provided a very salutary clinical lesson. So vascular are many adenomas that the wonder is that hæmorrhages are not more common.

Voss (1938) has published an excellent photograph of a pituitary adenoma full of recent blood. This had caused a severe subarachnoid hæmorrhage. In another case again (Olivecrona's, described by Hanke, 1939) there was a subdural hæmatoma surrounding a pituitary adenoma. My own, together with these two cases, are the only ones known to me in which bleeding has led to clear-cut signs.

I am enabled by the courtesy of Dr. Susman to illustrate another intact pituitary tumour with a suprasellar extension (fig. 10). This shows well the break-through of adenomatous tissue (here the chiasma is post-fixed), again compressing the 3rd nerve. This adenoma is no doubt malignant because the cavernous sinus is invaded. (This question is further discussed below.) Fig. 11 illustrates the cutting into the dorsal surface of the chiasma by the anterior cerebral arteries—that, in the writer's view, so important cause of visual loss in the inferior fields of vision in old-standing cases. Herniation of tumour tissue beneath an optic nerve itself has been already shown (fig. 6), but fig. 11 shows something further, not previously described, compression of the outer fibres of a splayed-out optic nerve by a trans-capsular sprout of adenoma. The patient was blind in that eye.

We may well wonder how far these herniations of tumour tissue are malignant. They are evidences of considerable tension and proliferative strength within the adenoma, but Case 7 has proved that even if there is such a protuberance of tumour within the cavernous sinus the patient may survive for years. When, however, the adenoma cells actually break into the cavernous sinus we should be justified in regarding the tumour as locally malignant, and call it a malignant adenoma.

The Malignant Adenoma

Reference has earlier been made to the nature of the pituitary adenoma, and emphasis laid on the probability of hormonal stimulation as the basic causal factor. It was pointed out that the early title of " strumous adenoma " had the advantage of suggesting an origin different from that of true blastomas. Yet once formed it seems probable that the adenomas pursue an independent existence (like blastomas). The reason why some grow slowly, some reach a certain size and then stop, whilst others grow increasingly, may never be known. Variability must depend on fundamental cell growth urgencies, the fact of which we may record but for which there is no particular reason. Any attempt to explain the reasons for growth must fail because the search brings us back to the nature of cell vitality itself, back, that is, to the final fact of growth behind which is nothing else, no further reason (what philosophy calls " the final irrelevance "). If we were able to prove that extra-pituitary influences of a hormonal or biochemical nature (the influences, in a word, of total bodily activity in which the pituitary, or what of it is undamaged, plays a part) were continuous in some cases and not in others we should still know no more of the actual *nature* of the growth process though we might be more satisfied to think that we had a *reason* for it. So far as we know such influences are not continuous and the adenoma is the by-product of a glandular activation which is over. In the eosinophilic tumours of acromegaly the parallelism between the toxicity of the adenoma and that of the thyroid in Graves' disease forces itself upon us, even to the point of inconsistencies in the size of gland and the severity of the toxic effects. In neither disease can we pretend to have a deep understanding of the principles by which the disorder of cell function has come about. What can be said is this, that as a result of stimulation to activity the endocrine glands of some persons may be driven to completely disordered action, and that such anarchical behaviour as regards the welfare of the organism as a whole is an inherent potentiality of these glands; beyond this fact search of the gland itself can reveal nothing. We must always be wrong if we study one organ alone for causality without regard to its relationship in total bodily economics.

It has been clearly shown by the cases already presented that some pituitary tumours come to burst their envelopes and to form smaller or larger sprouts through them. Often these are very small, and, unless they happen to press upon one optic nerve, locally on the chiasma, or to bulge into one of the cavernous sinuses, they do nothing to denote their presence. We should scarcely be justified in classifying such protrusions as signs of malignancy, for they give the impression of being mechanical

in origin, in the sense that they have developed as mere herniations because of the unequal density of the tissues which form the pituitary capsule. Yet there are two points that must not be overlooked; first, the fact that the capsule has been broken fulfils one of the conditions by which we classify malignant tumours, and secondly, the very fact that such breaches of the capsule have occurred indicate that the growth pressure inside the tumour must be high. It is true that cyst formation might raise the internal pressure, as might hæmorrhage, but the latter at least indicates a vessel structure which is tending to malignant type.

As for local infiltration of neighbouring tissue as a sign of malignancy, there are special difficulties. The pituitary is surrounded by structures which do not easily lend themselves to invasion. Superiorly the chiasma and the brain-mass are remarkably resistant to infiltration except by a tumour derived from their own proper tissues (cp. Trotter on the insulatory powers of the nervous parenchyma). Hence extension into the cavernous sinus and Meckel's cave are the only sign by which we can say that an adenoma shows malignancy ("malignant adenoma"). Such invasion envelops nerves and vessels without breaking through their sheaths. Malignancy is a term which must be given a different valency in different situations within the body. The ultimate death of the patient cannot be used as a standard, for within the skull a perfectly benign growth can be fatal. It is possible to trace through my own series of adenomas all degrees of growth tendency from the least to the most severe. Four of the most extravagant examples were Cases 9-12. In the background of this discussion lurks the question of pituitary carcinoma, and its relationship to the malignant adenoma. Some principles for definition must be laid down because these are, so far, lacking; the following are suggested:—

(1) The malignant adenoma is a tumour which has by its florid growth broken through its envelopes and is malignant only in the sense that tumour cells have entered into situations where they could not be if the capsule were intact. Malignant adenomas still retain a cell type which is similar to that in the smaller tumours. Invasion of the cavernous sinus would not kill, but its presence is highly significant of a continuous growth pressure or urge which probably eventually will do so. An adenoma may need years to produce such an extension. The term "malignant adenoma" is, in my view, somewhat artificial, but no more accurate designation suggests itself. This brings up very cogently the point raised earlier in this paper, that some adenomas stop growing after reaching a variable size. These are clearly non-malignant. A distinguishing line must therefore have a validity. Clinical signs alone do not always give evidence of invasion of the cavernous sinus (compare Cases 7 and 8).

(2) Pituitary carcinoma. This is a rare disease of which there is no example in this series. The diagnosis can only be made from the total effects of the tumour: (*a*) short history, (*b*) presence of extension, and especially of invasion of the cavernous sinus, (*c*) the presence of metastases[7] carried either from the cavernous sinuses into the blood-stream (e.g. Cushing's, Dudde's cases) or in the spinal fluid and subdural spaces (e.g. Cagnetto's, Cushing's cases), (*d*) from the cell type. There is no doubt that, as regards cell type, the Rathke pouch tumour is much the more easily recognized as having strong malignant tendencies. Erdheim himself classified these "hypophysenganggeschwülste" as existing in two forms, benign and malignant. The anterior-lobe carcinomas are more difficult to describe with a precision that can be clearly appreciated. This emerges very definitely from the attempts that have so far been made. A hard nodular cancer like that of the thyroid has not yet been met. It might exist. Pituitary cancer is said to be distinguished by the lack of pattern

[7] As for bone metastasis, I have operated upon one case, a woman aged 57, with a short history of paraplegia, and found a tumour invading the 6th thoracic vertebra that was returned histologically as a pituitary adenoma. She had no ocular or cerebral manifestations and necropsy was not obtained. Because of the uncertainty of present-day opinion as regards the possible pictures of malignant bone tumours, no certain conclusions can be drawn from this case. It is mentioned tentatively now.

in its cells, irregularity in cell grouping, highly chromatic nuclei, mitosis, and scant cell protoplasm. The more ordinary adenoma itself shows such great variations, as the work of Erdheim, Dott and Bailey, E. J. Kraus, and Berblinger clearly shows, that this description lacks a distinguishing crispness. In the long run metastasis must remain the most certain sign of malignancy; no argument is possible about cases of this sort. The limitations of the site of the metastasis possibly to a pituitary carcinoma have been indicated above. The malignant adenoma, on the other hand, marks the extreme of activity possible to an adenoma, short of actual metastasis, but includes the possibility of extension into the cavernous sinus.

Having accepted extension into the cavernous sinus as the most certain definition of a malignant adenoma, might not metastasis easily follow from the entrance of cells into the veins? If that were so then the boundary line between the malignant adenoma and pituitary carcinoma would disappear. It is the fact, however, that

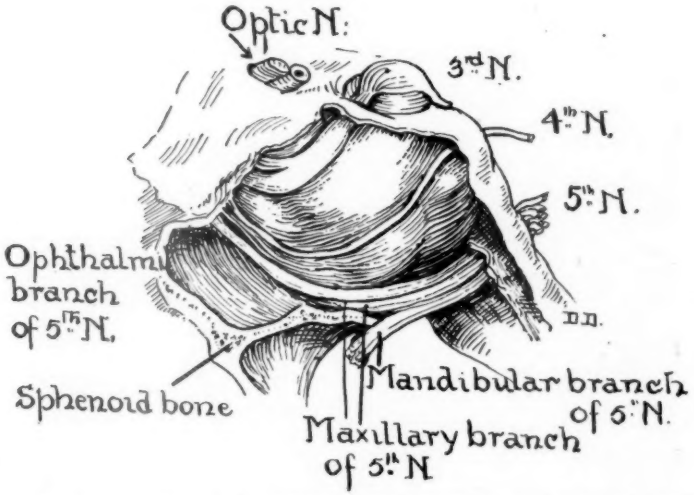


FIG. 8 (Case 9).—Dissection of cavernous sinus to illustrate compression of the nerves by an adenoma.

adenomas do not erode the venous sinuses; furthermore, in order that a metastasis should survive the cells must retain very great vitality. There is little doubt that for every metastasis that forms many must be destroyed by local reaction. The distinction here made between the types seems to be well founded. Pituitary malignancy is, therefore, of a type peculiar to the organ of its origin, and does not obey the general rules which we apply to carcinoma and sarcoma elsewhere. It illustrates something that is, in my submission, a most important and generally unrecognized fact—that all malignant tumours are specific to their sites and have life-histories and behaviours dependent on that origin. The pathologist tends to a simplification which does not exist in nature when he draws up rules which, he says, malignant tumours obey. To impose such a view is to imagine an abstraction separated from the actual facts of observation.

In Case 9 opportunity arose for dissection of the cavernous sinus and for verification of the relationship of the nerves in the cavernous sinus to the tumour. Although the history of amenorrhœa for twenty-four years would indicate that the adenoma had long been present, at post-mortem it was found to be of malignant type. This case, together with the remaining three malignant adenomas, will be described in brief.

Case 9.—E. G., female, single, aged 44, was admitted complaining of amenorrhœa and failing vision. Menstruation started at the age of 14 but was always scanty and irregular until it ceased at the age of 20. Failing vision. Bitemporal hemianopia. X-ray indicated a large chromophobe adenoma. No oculomotor palsy. Trans-sphenoidal decompression. Primary recovery. Death from sudden meningitis seven weeks later. Post-mortem: Adenoma found to infiltrate the left cavernous sinus. Fig. 8 shows the cavernous sinus dissected with the adenoma pressing heavily on the nerves contained in its walls. It may easily be imagined that diplopia should be a common event given an adenoma of any size.

Case 10.—N. R., female, aged 24, with an acromegalic appearance, was admitted to the Neuro-Surgical Service of the Manchester Royal Infirmary on October 3, 1931, complaining of failing vision and headache. She dated her illness back to five years ago when her menstruation ceased, diplopia developed, and she became extremely thirsty, passing large quantities of pale urine. Weber's syndrome. Left trigeminal anæsthesia. Glycosuria. Death. Necropsy: Huge suprasellar extension (retro-chiasmal) of a chromophil adenoma. Infiltration of left cavernous sinus and Meckel's cave into trigeminal root (*see* fig. 9).

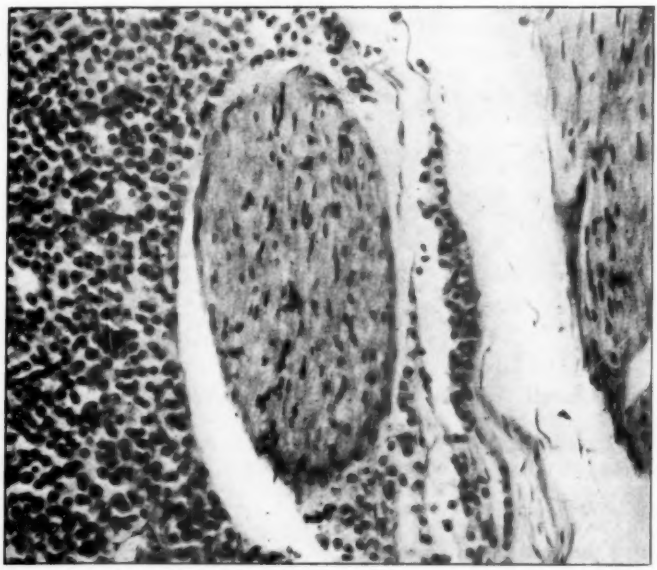


FIG. 9.—Malignant adenoma surrounding nerves in cavernous sinus.

Case 11.—Mrs. G., aged 29, was admitted to the Queen's Park Hospital, Blackburn, November 12, 1937, as a case of acromegaly. She was in very poor general condition and died a month later. She showed evidence of acromegaly and had failing vision, with spasmodic pains in the face. Death. Necropsy: Huge intracranial extension extending into posterior fossa. Infiltration of right cavernous sinus and cavum Meckelii.

Case 12.—R. G., aged 19, male, was referred by Dr. McKibbin of Liverpool on account of severe headaches and bilateral optic atrophy. Some eighteen months previously he had been admitted to a hospital on account of ophthalmoplegia of the left eye and defective vision. Malignant pituitary adenoma. Bilateral 3rd nerve paresis. Bilateral optic atrophy. Involvement of the left trigeminal nerve. Trans-sphenoidal verification. Deep X-ray therapy. Death from tuberculous pneumonia. Adenoma infiltrating both cavernous sinuses and spreading in the dura of the left middle fossa and over clivus into posterior fossa.

Ventriculography in Cases of Pituitary Adenoma

By the careful radiographic study of sellar shape and sellar size a very accurate measurement of the basal or intrasellar part of the tumour can be made. Its extrasellar extension can be gauged with approximate accuracy from (1) the visual acuity, (2) the visual fields. When acuity is bad and the field pattern either bizarre or difficult to interpret, and, in general, when there is anxiety as to the size of the tumour, pneumography is of great value. I have used it in 15% of the pituitary adenomas and tend to use it now more often still (especially by cisternal encephalography). It is only thus that a clear conception of tumour size can be arrived at. Two clear indications for its use can be laid down. First, when the visual symptoms are recent and yet the size of the sella suggests a very large tumour. Second, when the sella is not deeply excavated and yet the symptoms and signs indicate a chiasmal lesion of considerable size. Fig. 12 shows the latter point so well that further comment is unnecessary, save to add that great size is a strong discouragement to operation, especially when it discloses a massive tumour rather than a narrow-necked extension. Cairns (1932) has very properly pointed out the dangers of operating on long-standing tumours with poor vision and advanced optic atrophy, for improvement is unlikely and there is a strong prospect of fatality. With this view I am in complete agreement. Not only may the tumour be of parenchymatous type and difficult to remove, but even should it be soft the capsule fills with clot and a very stormy convalescence can, at best, be expected.[8]

Influence of Extension on Clinical Picture

The chief purpose of this paper has been to focus interest on the growth pattern of the adenomas. It would overburden any message that it contains if a long analysis of clinical variants were added ; the most important symptoms and signs have been given at length in the 12 illustrative cases. A brief commentary should suffice.

Endocrinal changes.—These are no different from those in the smaller tumours. In some of the patients with extensions or with massive tumours and long histories the somatic and skeletal alterations are more pronounced because the endocrinal factors have had longer time in which to act. Glycosuria, for example, has been more common. Whether this will prove to hold true when more cases have been collected remains to be seen, for it is a little surprising that it was so. It might have been thought to have been due more to the acuteness of the endocrinal upset than to its duration, and that may be true even with the present cases.

The visual fields.—The importance of post-fixation of the chiasma on the visual field pattern was shown by Case 3, where it was normal in spite of the presence of a large tumour. Papilloedema was present in this case at one time. Wagener, Woltmann, N. N., and Love (1939) have recorded a similar case, also with post-fixation. Except in cases such as these, prefixation is difficult to establish except by the ventriculographic method, which has an important, and hitherto unsuspected, usefulness, in this respect.

The effects of prefixation have been mentioned. Balado (1937) pointed out that macular sparing was the rule with the average bitemporal hemianopia of pituitary enlargement. He agreed with Cushing (1930) that the macular fibres decussate in the posterior part of the chiasma. The converse effect of bilateral macular scotomas should mean that the tumour was either behind the chiasma or that it extended well back beneath it. Cushing had come to much the same opinion as a matter of

[8] The reason why these old-standing cases are so unpropitious can be summarized as (*a*) because the tumour is very likely to possess an extension and (*b*) for reasons remarked earlier the main tumour mass is likely to be retro-chiasmal. Even if there is no extension in its anatomical sense the tumour will usually be massive and irreparable damage to the optic nerves and chiasma will have been occasioned on the one hand by tumour pressure, on the other by the cutting into the chiasma of the anterior cerebral and communicating arteries.

observation at operation, an idea supported by Henderson's later study of the same material. My own cases confirm this view, though it must be admitted that the intrachiasmal course of the macular fibres is not yet known with complete certainty. The possibility of a large tumour forming behind a pre-fixed chiasma has been alluded to, as well as the possibility of tract, rather than chiasmal compression occurring in such cases with a resulting homonymous defect. Fig. 5 shows that prefixation is not an absolute necessity to homonymous defects; this specimen is a valuable corrective to speculative reasoning. No example of hemianopia due to indentations of the temporal lobe has occurred in this series. Study of this figure suggests something more. Since the lesion as it passes into the temporal lobe must always compress the optic tract, distinction between the two types would seem to be invalid. When the chiasma is more normally placed an extension or a massive tumour leads to the deep cutting of the anterior cerebral arteries into the dorsal surface of the

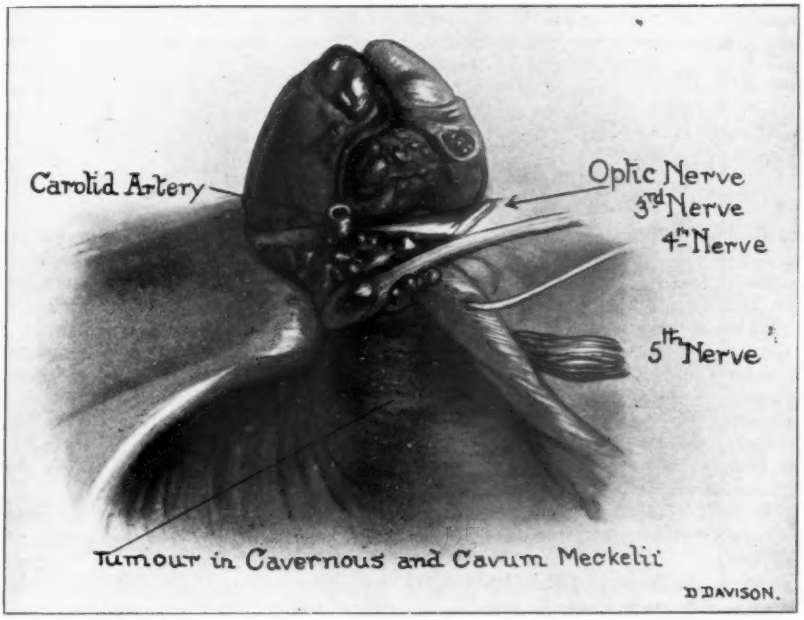


FIG. 10.—Malignant adenoma invading cavernous sinus and surrounding carotid artery. Compression left third nerve.

chiasma (*see* fig. 11). This has always seemed to me to be a much more probable reason for the cutting off of the fields of vision inferiorly than a supposed kinking of the optic nerves against the upper margins of the optic foramina. Indeed, what with the tumour below and these arteries constricting the chiasma above, it is remarkable that the chiasma is not earlier completely blocked to light impulses. The importance of local protrusion in producing a unilateral central scotoma has been mentioned.

Diplopia.—Diplopia is not an indication of extension. It is a common symptom. It is due to pressure on the medial walls of the cavernous sinuses, much thinner than the outer. Pressure on the oculomotor nerves leads to that slight inco-ordination

of ocular movements which is sufficient to cause diplopia without there being any easily discernible lack of parallelism of the eyes.

Oculomotor palsy.—This is generally, but not invariably (cp. Case 7), a sign of invasion of the cavernous sinus, a sign that is, in the classification suggested above, of the "malignant adenoma". The 3rd and 4th nerves suffer much more often than the 6th, which is protected from pressure by the carotid artery, on the outer side of which it lies. Cases besides the three here have been reported by Strumpell, Borchard, Castiglione, and others (*see* Atkinson, 1932), and by Sjöquist, 1936. As in Case 10 it may be associated with hemiparesis as Weber's syndrome.

Trigeminal anæsthesia.—Three beautiful examples have been given of infiltration of the trigeminal root by malignant adenomas. No purely benign adenoma ever produces it. The importance of trigeminal hypoæsthesia as an indication of the nature of the tumour cannot be over-estimated.

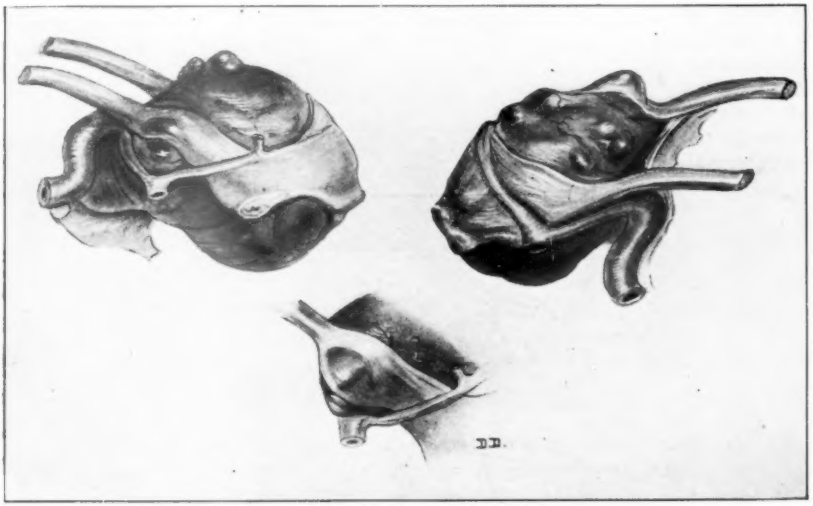


FIG. 11.—Chromophobe adenoma, herniation of adenoma compressing the outer fibres of left optic nerve (left eye blind). Compression by anterior cerebral arteries on dorsum chiasmatis.

Epilepsy and mental changes.—Fits would be expected in at least half the cases with frontal and temporal extensions. With temporal extension a lesion situated in the sella and passing outwards is ideally situated to impress the uncus. It is significant that uncinate fits were an early feature in the two cases with temporal extensions in this series. The frontal fits were of the usual pre-frontal type, without aura or with dizziness only, and the convulsions were generalized.

Hypothalamic signs.—The lethargy and mental hebetude described by so many writers as characteristic of pituitary tumours are, in the writer's opinion, overdue for correction. It is by no means a constant or even a common feature with small adenomas, whatever their type. It cannot therefore be due to the endocrinal disorder itself, except in a minor form. When it becomes a feature of the patient's state it is due either (*a*) to extension upwards into the cranial chamber, or (*b*) to loss of visual perception. In the former case the retardation is due to neural or circulatory

abnormalities produced by the tumour mass, in the latter to that general slowing down which is so characteristic of severe visual impairment. The effects of loss of vision in animals on total bodily activity have been investigated in recent years and found to be of great importance. Such contribution to the state as is made by the endocrinal disturbance of hypopituitarism must be of the same order, for lack of the normal hormones clearly has general effects and cannot be thought of in pituitary terms alone. It may be urged that hypersomnia as distinct from lassitude and a general preference for idleness predicates a lesion of the hypothalamic sleep centre (*see*, for example, Globus 1940). To differentiate between hypersomnia and general hebetude is artificial. They must all be part of one general process. In Case 1 where hypersomnia was a feature, there was a localized hypothalamic extension (fig. 3), but also pressure was very high within the skull. It is not intended to deny that there is an area in the hypothalamus the destruction of which leads to hypersomnia, for the fact that lesions there have led to somnolence is well attested. One thing is certain, that the areas destroyed cannot have been the sleep centre, since what does not exist cannot function, as Hughlings Jackson repeatedly insisted.

Cerebrospinal fluid protein.—The high quotient of the protein in the cerebrospinal fluid may have been observed by the reader in two of the cases quoted. It will be worth while to give some of the results, especially because no information on this point exists.

In the following table it will be seen that the larger the tumour the higher is the cerebrospinal fluid protein.

LUMBAR C.S.F. PROTEIN ESTIMATION.

	Sex	Age	Proteins mgm.%
Acromegalics	F.	47	45
	M.	50	50
	F.	42	100
	F.	35	20
Chromophobe adenomas			
A. Small tumours ..	M.	60	45
	F.	48	35
	M.	29	25
	F.	52	30
	M.	42	65
	F.	39	25
B. Large tumours ..	M.	57	140
	M.	54	100
	M.	60	70
	F.	46	95
	F.	55	160
	M.	34	150
	M.	41	200

There is a protein rise whenever a tumour has access to the cerebrospinal fluid, whenever it has the opportunity of excreting its metabolites into it, whenever capillary oozing may be contributed to it. Surface area must play a considerable part, and a small tumour with a high protein cerebrospinal fluid count is probably a very active one.

Effect of extension on operative mortality.—In most cases with a large extension operation is a course of doubtful wisdom. In a series of 128 adenomas, the writer's own mortality was 2·0% for the small adenomas (one death from extradural post-operative hæmatoma, one presumably from avertin) for 98 cases. In those with extensions the mortality was 33%, 4 out of 12 cases operated upon. The other cases with extension were left alone. The operation on the small pituitary adenoma is so gentle a procedure that theoretically there should be no mortality; actually

the mortality is slight. The danger of delaying operation whilst prolonged X-ray therapy is tried in an early and favourable case is clear. If the adenoma grows and forms extensions the risk of operation increases. Finally, operation on old-standing and massive tumours is not often profitable to the patient. The severe changes in the chiasma brought about by prolonged and increasing compression are irremediable. The study of some of the illustrations shows the hopelessness of their problem.

It is impossible to give an accurate percentage figure of incidence of extrasellar extension; Henderson states that there were 51 in Cushing's 365 adenomas (about 1 in 7). There were 18 cases in the present series (of which 12 were described), the only truly verified examples in 128 cases, a similar incidence. I should estimate it therefore as occurring in some 14% of adenomas, a fairly high ratio.

FIG. 12.—Encephalogram of suprasellar extension. No depression of sellar floor.

CONCLUSIONS

The foregoing account has been an attempt to broaden the conventional description and to correct too didactic a formulation of the nature of the pituitary adenoma, to account for variations in symptomatology, and to give reasons why operation is sometimes, though rarely, attended by ill-success. Detailed information on all the relevant points does not yet exist in sufficient volume to allow of an infallible interpretation of the biological history of these tumours. None the less, even in the malignant cases, the histories tend to be so long that the adenomas remain a thoroughly worth-while field of surgery. All writers hitherto have shown a disinclination to define exactly the criteria of pituitary malignancy. So far as reliance is placed on differentiation by cell structure alone ambiguity would have remained. An attempt has been made here to designate malignancy with more precision. It has been shown that the growth tendency of the adenomatous cells is highly variable, and it might be concluded that such tumours as tended to produce massive intracranial extensions were all essentially malignant, that "extension" is but an alias for "malignancy". This is not necessarily true, for size is not an index and unless there is either invasion or metastasis a tumour, whatever its size or ramifications, or whatever its cellular structure, must be considered to be benign.

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Section of Otology

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[*March* 1, 1940]

Further Clinical Observations on the Nature and Treatment of Ménière's Disease

By A. J. Wright (Bristol), F.R.C.S.

On November 5, 1937 [1], I presented to this Section the results of a clinical research based on the detailed investigation of a series of cases of aural vertigo. On that occasion I formulated two broad conclusions. The first of these was that such cases represent a defined entity, i.e. that we may correctly speak of Ménière's "disease" and not of Ménière's "syndrome". The second was that this disease consists essentially of a lesion in the labyrinth secondary to infection usually to be found in the nose, mouth, or throat.

Since the publication of this paper, considerable support has been afforded to the first conclusion, that Ménière's disease exists, by the publications of Crowe [2] on the clinical side and Hallpike [3] on the histological. On the other hand, in regard to the second conclusion, Crowe denies the importance of infection in the ætiology; and the beautiful histological work of Hallpike has demonstrated changes which cannot be regarded as inflammatory in the ordinary sense of the term. I feel, therefore, that the infective ætiology must be as yet regarded as generally unproven. Being myself convinced of its truth, however, I am to-day presenting further evidence in the way of clinical results, as it is probably by the accumulation and presentation of these that the truth or otherwise of the thesis will be established. The results are those obtained in a series of cases in which infective lesions have been treated surgically. Such treatment has consisted in the removal of tonsils, the removal of teeth, and the operative drainage of accessory nasal sinuses. The evidence of infection in the tonsils has been provided by the history of previous inflammatory attacks combined with the naked-eye examination of the organs. As far as the mouth is concerned, the treatment has been radical. All dead or possibly infected teeth have been removed, and, where obvious periodontal infection has existed, the mouth has been cleared. Dental treatment has in all cases preceded nasal or tonsillar. In regard to the nasal sinuses, the diagnosis of infection was based on ordinary clinical and X-ray examination confirmed by proof puncture. The operations carried out consisted of the intranasal clearance of the ethmoid where indicated, and a Caldwell-Luc operation on the antra.

During the course of an independent bacteriological investigation by Dr. A. L. Taylor, the nature of the infecting organisms in the removed tonsils was investigated. Of these the very great majority showed an infection with a *Streptococcus viridans*. This finding perhaps lends some support to the infective thesis.

A minimum period of six months has in all cases been allowed to elapse between the completion of treatment and the assessment of the result, and to maintain the experimental value of the cases, no other treatment of any sort has been employed.

Results

The effect of treatment on the three symptoms of vertigo, deafness, and tinnitus, has been recorded separately, the terms " cured ", " improved ", " unaltered ", and " worse " being employed. The result as regard each symptom was only recorded where reliable evidence was available.

The figures are as follows :—

Vertigo.

Total, 84 cases.

Cured	70
Improved	4
Unaltered	6
Worse	4
	84

i.e. 10 failures, 74 successes = 88%

In the 70 cases noted as " cured ", the patient states that there is an entire absence of vertigo. In the four cases noted as " improved ", attacks have ceased but some general unsteadiness is still mentioned.

Deafness.

Total, 68 cases.

Cured	2
Improved	46
Unaltered	14
Worse	6
	68

i.e. 20 failures, 48 successes = 70%

The reason for the smaller total number of results as far as deafness is concerned is that cases were only recorded in which definite evidence could be obtained, usually in the form of hearing tests by myself. Here " cure " means the return of the hearing to the normal and in each of the two cases it is based on tests with the audiometer. The fact that the figures in regard to hearing are less good than those for vertigo is to be expected, since deafness may simply indicate structural damage and not a still existing progressive lesion.

Tinnitus.

Total, 57 cases

Cured	9
Improved	25
Unaltered	17
Worse	6
	57

i.e. 23 failures, 34 successes = 59%

The smaller number recorded in regard to tinnitus is, I am afraid, to some extent due to faulty note-taking. That the figures would not be so good was to be expected and I was surprised to find that improvement or actual cessation took place in so large a number, i.e. more than half. This symptom frequently persists even after destruction of the labyrinth or section of the 8th nerve.

The figures in regard to the site of the infective lesion or lesions dealt with are as follows :—

	Totals.
Tonsils	68
Teeth	27
Nasal sinuses	20

The figure in regard to teeth is rather misleading as a certain number of cases had had teeth removed shortly before I saw them.

A single lesion was dealt with in 56 cases and two or more in the remaining 28, i.e. one third.

Where multiple lesions were dealt with the figures were :—

Sinuses, teeth, and tonsils ..	3
Sinuses and teeth	5
Teeth and tonsils	11
Sinuses and tonsils	9

Criticism of Results

The finding of 88% successes, as far as the vertigo is concerned, if accepted, would seem to be very significant. The lower figures of 70% for hearing and 57% for tinnitus would, as I have already said, seem to be what one would expect, as these two latter symptoms may simply indicate structural damage and not a still existing progressive lesion.

I have tried to consider these figures from the point of view of the obvious criticism that the apparent improvement may be due to the normal course of the disease which, as we know, is often very irregular. Would 88% of cases, if untreated, show a cure if investigated after a minimal interval of six months ? I believe not. In support of this view, I find that in this series the average duration of the disease before the cases were first seen was six years. Also, in a recent paper by Walsh and Adson [4] from the Mayo Clinic on the comparative results of medical and surgical treatment of Ménière's disease, figures are included which seem to me to be of some significance. Thus, of 152 patients treated with a low salt intake with or without the addition of medication, only 34% were completely free from vertigo. On the other hand, it is interesting to note that in a smaller group of 23 cases described as having been treated by " other general measures ", 61% became free of vertigo. As to the nature of these " general measures ", I was even more interested to observe that " elimination of foci of infection and the use of sedatives " was all the detail given. It really seems as if the authors had unwittingly provided evidence in support of the infective ætiology.

Detailed consideration of the 10 cases classed as failures would seem to furnish further support to the concept of an infective ætiology. Thus, of the 10 cases, no less than seven were the subject of nasal sinus infection and eight of multiple lesions, these figures of 70% and 80% comparing with 25% and 33% for the whole series. Thus, multiple lesions and nasal sinus infections, both of which are difficult to cure by surgery, are found in a high proportion of the failures. Also, of the 10 cases, one is now the subject of generalized eczema and fibrositis, another has been in hospital recently with sciatica, and a third has a chronic progressive choroiditis. Bacterial allergy is pronounced in three of the cases, and four of them have had operations directed to nasal sinus infections by other surgeons than myself and before the onset of the labyrinthine lesion. It may be of interest to record that four of the failures subsequently obtained relief from an alcohol injection through the oval window.

General Discussion

I think it would be fair to state that there is no general principle in medicine on which opinions are more divided than on the ætiological importance of infection in chronic disease. As far as Ménière's disease is concerned, the literature provides

many examples of nerve deafness or vertigo clearing up following the surgical treatment of infection in the nose, mouth, or throat. In this respect, the articles of McKenzie [5] and McMurray [6] seem to me to be particularly important. But Crowe, whose article has already been referred to, while giving a picture of the complaint similar to my own, denies that infection is in any way a factor in the ætiology of the changes in the labyrinth. These extreme divergencies in opinion would seem to call for some explanation which I believe to be as follows : It must be appreciated that if infection be accepted as the cause, it is not by any means always possible to get rid of such infection, and therefore a failure to achieve a cure as a result of treatment in an individual case is not necessarily proof that the conception is wrong. In fact, clinical examination of failures will usually show a persistence of infection. Also I believe that the use of the term "*focus*" of infection has been responsible for the occurrence of many failures in treatment with, as a result, a rejection of the hypothesis of an infective ætiology. The term focus seems to imply a single localized and perhaps shut-up centre of infection. The more, however, that the idea of such an occurrence, in all cases, be given up and a careful investigation be made for the existence of infective lesions generally, the better will be the results when the appropriate treatment is supplied. The following case well illustrates this fact and the complexity of the problem which is sometimes presented :—

The patient, a woman aged 56, when first seen had had severe attacks of vertigo with deafness and tinnitus for eighteen months and was unable to go about alone. Her teeth had been removed nine months after the onset of the complaint. Examination disclosed a stinking and almost certainly dental infection of one antrum and this was operated on. During the next few months the condition became worse and a peri-articular arthritis of one shoulder developed. Seven months after the antral operation, tonsillectomy was performed. Some degree of improvement took place for a few months but the attacks still continued although with less severity. One year after the tonsillectomy, the gall-bladder was removed for cholecystitis. Within the next three months the attacks faded out, the hearing improved, and for the last eight months the patient has been apparently cured.

Thus we have successively the surgical treatment of dental infection antral infection, tonsillar and gall-bladder infection, with eventual relief.

Again, a lack of thoroughness in following out the conception is frequent. This is sometimes unavoidable as the patient may refuse to submit to, say, the complete clearance of the mouth, or to the removal of the tonsils. This half-hearted acceptance of the idea of infection is, however, often that of the doctor and not of the patient. The complaint is so distressing that most patients will submit if the doctor is convinced.

Finally, opinions may differ as to whether infection exists or not, particularly in the case of the tonsils.

Apart from the results of treatment, some other evidence linking up infection with Ménière's disease is provided by : (*a*) The occasional initiation of the disease by surgical treatment of infection. Thus, on two occasions I have seen cases, the onset of which followed immediately on an extensive clearance of the mouth. Such a happening is recognized as occasionally taking place in regard to the eye. (*b*) The occasional simultaneous onset of other lesions such as fibrositis with Ménière's disease, suggesting a common ætiology. (*c*) The existence of gross infective lesions in combination with Ménière's disease in a higher proportion than mere coincidence would provide.

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DISCUSSION ON FUNCTIONAL DEAFNESS

Sir Arthur Hurst : I believe that in many cases of deafness among civilians there is a functional element, and this may also be the case in a small proportion of deaf-mute children. My interest in the subject is a result of the many cases of severe hysterical deafness which came under my observation during the last war.

The noise and concussion produced by the explosion of a shell of high power in the near neighbourhood frequently caused deafness. The patient became dazed or unconscious as a result of the explosion, and when his mind became clear again he discovered that he could not hear. Both ears were generally affected, but the one on the side more exposed to the explosion was often deafer than the other. The initial deafness was doubtless due to concussion of the internal ear, as it was sometimes accompanied by vertigo and temporary nystagmus, but there is no evidence that this was ever associated with hæmorrhage into the internal ear. One or both drums were often perforated owing to the sudden enormous change in atmospheric pressure. Such a perforation did not greatly affect the prognosis, as the tear generally healed, and if no hysteria developed normal hearing was restored. Sometimes, perhaps, the ossicles were dislocated by the force of the explosion, in which case some permanent impairment of hearing would result. The deafness might pass off in the course of a few hours, but more frequently it lasted for a few days. If it persisted for a still longer period, it was almost always hysterical, at any rate in part. The initial concussion deafness made such an impression on the mind of the soldier that, on coming to himself, whether he had actually lost consciousness or not, his first thought was for his hearing, and he might be so convinced that he was permanently deafened that he became actually deaf as a result of auto-suggestion. This was especially likely to be the case if for any reason the idea of deafness had previously entered his mind ; it was for this reason that a large proportion of cases occurred in men who had old disease of the ear.

The temporary deafness, which is a familiar condition in peace-time among gunners and other people exposed to the frequent repetition of loud noises, may in the same way become perpetuated and exaggerated by auto-suggestion.

Lastly, organic deafness, especially if the onset is acute, as in that due to involvement of the auditory nerve trunk in cerebrospinal meningitis, may remain complete after the disappearance of the active disease has been followed by sufficient restoration of the damaged structures for a certain amount of hearing to have returned. This, again, is due to auto-suggestion, the final deafness being organic with a superadded hysterical element, which is capable of removal, like all hysterical symptoms, by psychotherapy. If left untreated without any encouragement, and especially if steps are taken to teach the patient lip-reading, he will become more and more convinced that he is permanently deaf.

Hearing does not consist merely of the perception of impulses conveyed to the brain when the ear is stimulated by sound waves. It is an active process, and in order that sounds may be heard the individual must listen. Inattention during a dull sermon results not only in absence of perception of the words said, but of total deafness to the sound of the preacher's voice. It is clear that impulses to the cortical centre of hearing must be actually interrupted by inattention. The most satisfactory theory is that in the act of listening the resistance at the various synapses in the auditory path is in some way diminished. In inattention the resistance is increased.

In animals there is an obvious motor element in listening in addition to the sensory element just considered. This is seen in the movements of the external ear, which is most obvious in those which depend upon flight, prompted by the acuity of their hearing, for safety from their enemies. If one pays attention to one's own sensations in the act of listening, it appears as if some active process were taking place in the ear. This probably consists in the simultaneous contraction of the stapedius

and tensor tympani muscles, which exert tension on the chain of ossicles in opposite directions. Their function appears to be to regulate the balance of the stapes, and so modify the intravestibular pressure that the cochlea may act at its maximal efficiency. The small muscles of the external ear are generally regarded as rudimentary and functionless structures in man. They are, however, as well developed in man as in apes. On closely watching the ears of people who were listening intently, I found that a definite movement always occurred. In some cases the outer edge of the auricle moved outwards and forwards on listening to a sound in front, and inwards towards the side of the head on listening to a sound behind. The most vigorous movements were seen in a man who could move his ear voluntarily, and who was also aware that he moved it when he listened intently. It is, of course, obvious that these movements are mere remnants of the big movements in animals, which have the object of concentrating as many sound-waves as possible in the external auditory meatus, but they are sufficient to indicate that listening is an active process on the motor as well as the sensory side.

When a man is temporarily deafened by a loud noise or by some recoverable disease, he finds that he is unable to hear, however much he tries, and consequently after a time he gives up trying. That is to say he ceases to listen, and when the cause of the deafness at last disappears, he has become so convinced that he cannot hear that he makes no further attempt to listen. Although the sound vibrations reach his ears in the normal way, they do not give rise to the slightest auditory sensation because of this inattention ; he is then suffering from hysterical deafness, the inability to hear having been suggested by the original organic, though temporary, deafness. Severe hysterical deafness developed in a soldier while he was the only Englishman in a German prison ; he ceased to pay attention to what was said, as he could understand nothing, and in time he ceased even to hear the unintelligible conversation of his companions. His hysterical deafness was rapidly cured by psychotherapy when a year later he came into Seale Hayne Hospital.

In hysterical deafness the resistance at all the cell-stations in the auditory path to the cerebral cortex is apparently increased. Further evidence for this follows from a study of the auditory-motor reflex. A sudden noise causes an individual to jump and often to blink, and the pupils dilate. An officer, whose left motor cortex had been almost completely destroyed by a shell wound, went to the *Man Who Stayed at Home* about four months after he was wounded. His right arm jumped violently when the gunshot rang out on the stage, although no trace of voluntary movement returned until three months later. The reflex must therefore be subcortical. In certain war neuroses of emotional origin the resistance at the synapses is diminished and an extreme degree of hyperacusis develops ; the auditory motor reflex is then exaggerated, and jumping continues during sleep and deep hypnosis, although the patient does not hear the noise which induces it even in a dream. The afferent part of the reflex is thus also subcortical, the reflex being quite independent of actual hearing. Experiments on cats by Sherrington and Forbes (1914) have proved that the auditory-motor reflex is a function of the mid-brain. Sounds, especially barks, yowls, and whistles of birds, excited orientatic reflex movements of the pinna and neck after the complete removal of the cerebral hemispheres, striata, and thalamus. Reflex movements expressive of anger and aggression—lashing of the tail with bristling of its hairs, and flexion and extension movements of the limbs—were also produced. In our cases of complete bilateral deafness the auditory-motor reflex was absent, but returned simultaneously with the restoration of hearing as a result of psychotherapy. A very nervous but totally deaf mute remained completely unmoved, never jumping or showing a flicker of his eyelids during one of the severest thunderstorms I have known, and yet the next day he was completely cured by suggestion under partial anæsthesia.

The abolition of the auditory-motor reflex in absolute hysterical deafness makes

it clear that in hysterical deafness changes must take place at the level of the reflex, or still lower—in the auditory nucleus or one of the intermediate cell-stations, the superior olive and the nucleus of the lateral fillet, or perhaps in all. The persistence of the deafness during hypnosis and natural sleep shows that when the inattention of hysterical deafness has lasted for a considerable period, increased resistance at the synapses is more profound than that which normally occurs during deep sleep, in which the synapses can always be forced by a loud noise.

Diagnosis

In observations carried out at Netley with E. A. Peters (1917) we found it necessary to discard almost all the criteria formerly used in the diagnosis of organic deafness from deafness due to hysteria or malingering.

(1) *History.*—Complete bilateral deafness following the explosion of a powerful shell was generally hysterical.

(2) *Other evidence of hysteria.*—Hysterical symptoms may develop in apparently normal individuals if the suggestion which provokes the symptoms is sufficiently powerful. No more powerful suggestion of deafness could be imagined than the organic but temporary deafness caused by the noise of an explosion in the immediate neighbourhood. It is therefore not surprising that hysterical deafness occurred almost as frequently in soldiers who had no personal or family history of neuroses as in those with a neuropathic predisposition. Deafness was consequently the only hysterical symptom in many of the cases. When, however, the onset was associated with extremely terrifying circumstances, and the patient was of a nervous type, some of the physical results of fear, such as mutism and tremor, were often perpetuated as hysterical symptoms. Thus hysterical deaf-mutism was quite common.

(3) *The supposed association of hysterical anæsthesia of the external ear with hysterical deafness.*—Ever since Briquet in 1859 described the association of hysterical deafness with anæsthesia of the external ear, this has been regarded as an almost constant phenomenon. Symns, Gainsborough, and I (1918) tested the sensibility of the external ear in 29 soldiers, all suffering from organic deafness, due to various causes and of varying degrees of severity. The ears were first touched lightly with some wool, sometimes beginning with the deafer ear, sometimes with the ear which was less deaf or normal; at the same time the patient was asked, "Which side do you feel more distinctly?" A similar comparison was then made between each ear and the cheek on the same side. In 28 out of the 29 cases hearing was distinctly better on one side than the other, and in several the latter was normal. 18 of the 28 had partial anæsthesia, and four had hyperæsthesia of the affected ear; the better ear was normal in every case. The six cases of asymmetrical deafness, in which no anæsthesia or hyperæsthesia was found at the first examination, were then examined again, but a gross form of suggestion was now employed, the patient being asked the following questions: "You feel my finger less clearly when I touch this ear (the deafer one) than this one, don't you?" and "You feel me touch this ear (the deafer one) less clearly than your cheek, don't you?" Four out of the six patients answered "Yes"; in the remaining two the degree of deafness was very slight. In several of the patients anæsthesia was found to be very well marked, and was associated with complete or partial analgesia. So real was this loss of sensation that one patient was subsequently seen putting a pin through the lobe of his ear for the amusement of the other men in his ward.

In a case of severe bilateral hysterical deafness examined in the same way, both ears were found to be completely anæsthetic. In a second case, in which one ear was totally deaf owing to organic disease and the other had been totally deaf owing to hysteria, but was now only partially deaf as a result of psychotherapy, the organically deaf ear was found to be anæsthetic, and the hysterically deaf ear was

normal, corresponding with the fact that the deafness of the former was much more severe than that of the latter.

It is thus clear that the supposed association of hysterical anæsthesia of the external ear with hysterical deafness is a complete fallacy, and that anæsthesia is likely to occur in a deaf ear if looked for, whether the deafness is organic or hysterical, so long as the individual is sufficiently suggestible and not too well educated. Thus in all the above cases the patients were soldiers who had been on active service, and our experience showed how suggestible the majority of war-worn soldiers are, even in the absence of any hysterical or other nervous symptoms.

Ten well-educated individuals, who were asked whether they would expect any difference between the sensibility to touch in the two external ears if they were deaf on one side only, replied in the negative. On the other hand, seven poorly educated men all replied in the affirmative. The difference is simply due to the fact that no intelligent man would expect his external ear to be anæsthetic if he were deaf, but a man of less education would act upon the suggestion implied in the question without criticizing it. The greater frequency of grotesque hysterical symptoms among hospital than private patients, and among private soldiers than officers, is doubtless due to the greater intelligence and greater development of the critical faculties in the latter.

(4) *Bone and air conduction.*—When deafness is not absolute, a tuning fork can still be heard by bone conduction (positive Rinne's test). This shows that the deafness does not depend on changes in the middle ear, even when these are present. But it does not distinguish between the nerve deafness due to organic disease and that due to hysteria. Moreover, the test can only be applied in the slighter cases, as in many instances deafness is absolute and no hearing is possible, whether the sound is conducted by bone or through the air.

(5) *Auditory-motor reflex.*—In absolute deafness, whether due to organic disease or hysteria, the auditory-motor reflex is absent, but in partial deafness, whether organic or hysterical, if a sound can be heard at all, it may produce a reflex. If a reflex is present, but the patient says he can hear nothing at all, he is probably a malingerer, but so long as he admits that he can hear something, the test does not help in distinguishing between organic deafness, hysterical deafness, and malingering.

(6) *Persistence during sleep.*—As hysterical symptoms are due to suggestion, it might be expected that they would not persist during sleep. This is true of hysterical paralyses and contractures. I also saw several deaf-mutes and one aphonic patient, who talked in their sleep, and a man with hysterical amnesia had nightmares referring to his period of amnesia. But hysterical deafness is an exception, as I found it quite impossible to wake two of my patients, who were suffering from total hysterical deafness and were sleeping in a hut by themselves, by shouting or banging a pail with a poker within a foot of their heads. In one patient a slight twitch of the eyelids was sometimes observed with a particularly loud noise, but not in the other. It seems probable that a malingerer could be detected by this test, as he would certainly wake if a loud noise was made when he was asleep.

(7) *Effect of hypnosis.*—I had expected that hearing would return in hysterical cases during hypnosis, but I found it quite impossible to make deaf patients, whom I had deeply hypnotized, obey any command or show any signs of hearing, and no auditory-motor reflex was produced.

(8) *Character of the voice.*—In almost all cases of severe deafness due to organic disease the character of the voice changes. It is difficult to understand why there should be any difference in the effect of total deafness on the voice, whether it is organic or hysterical, as the change is simply a result of the patient's inability to hear his own voice. Although in some of our hysterical cases the typical voice of the organically deaf developed, the majority showed no change in timbre or intonation.

(9) *Lip-reading.*—When a deaf man teaches himself lip-reading, his deafness must be of a high degree. Several patients with hysterical deafness unconsciously learnt it with remarkable rapidity, so that it cannot be regarded, as has been suggested, as a sign of organic disease. On the other hand, it is very unlikely that a malingerer would ever learn lip-reading.

(10) *Vestibular symptoms and reactions.*—Disturbances in the vestibule as a result of concussion may cause spontaneous nystagmus, which may be accompanied by giddiness and staggering, but these symptoms rarely last for more than a few hours. We found that the only test upon which almost complete reliance can be placed in the diagnosis of absolute hysterical deafness from absolute organic deafness is the presence of normal vestibular reactions to the rotation and caloric tests in the former and their loss in the latter. The vestibular reactions are entirely beyond the control of the will, and it is therefore inconceivable that they should disappear as a result of suggestion. As hysterical symptoms are always caused by suggestion, the vestibular reactions must remain unaffected in hysterical deafness. On the other hand, it is highly improbable that any organic lesion could damage the cochlea or the cochlear nerve or nucleus on both sides sufficiently to cause total bilateral deafness without at the same time damaging the vestibules or vestibular nerves or nuclei, so that total organic deafness is almost certain to be accompanied by deficiency in the vestibular reactions.

Treatment

When hysterical deafness is associated with mutism it requires no special treatment, as hearing almost invariably returns spontaneously when speech is restored. The patient should be told that directly he speaks he will hear his own voice, and that he will then hear everything clearly. There is rarely any difficulty in curing the mutism by simple explanation and persuasion, though in our earlier cases we occasionally resorted to the suggestion produced by applying faradism to the larynx or making the patient excited with an anæsthetic.

Uncomplicated hysterical deafness is much more difficult to treat, and for a time our results were less satisfactory than in any other hysterical condition. For this reason we were induced to employ various forms of suggestion, although we realized that the methods were not really satisfactory. Suggestion under hypnosis was never of any use, as the patient remained deaf while hypnotized, and consequently heard none of the suggestions which were made to him. Electricity as a means of suggestion was sometimes successful, but often failed. In a number of cases of absolute bilateral deafness, which had resisted all other forms of treatment for some months, we performed " fake " operations, making a scratch behind the ear in the incompletely anæsthetized patient. This method of treatment was not invariably successful, and at the best it was not one which could be regarded as desirable, as it is much more satisfactory for the patient to understand how he has been cured than for him to be fooled into a cure by gross suggestion. With increased understanding of the psychological basis of hysterical deafness we were able during the last year of the war to cure a large majority of cases by the most rational form of psychotherapy—explanation, persuasion, and re-education. The patient is made to understand by written explanations how he has become deaf, and how the original cause of his deafness has now disappeared : as the deafness was at first organic, he could not hear, however much he listened, and consequently after a time he ceased to listen. He is then persuaded to listen intently, and is taught that listening is just as active a process as moving, and requires a conscious effort on his part until it becomes automatic once more.

Even when a man has completely recovered his hearing, it may take some time before he becomes accustomed to the new conditions, especially if he has been deaf for a long period. When caught unawares he often fails to hear, though directly he

perceives he is being spoken to he listens, and can then hear even with his eyes closed, so that lip-reading cannot help him. In severe cases he may hear the sound of the voice without being able to distinguish what is said. Re-education is then required in order that the sounds he hears, but at first cannot interpret, can be understood, that words which must at first be repeated separately from each other can be used in continuous sentences, and that the voice which must at first be raised can become progressively more quiet. A similar method of re-education can be employed for many people suffering from some incurable form of deafness who can in this way be taught to make the most of what powers of hearing they still possess.

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Dr. Emanuel Miller : We must all express our indebtedness to Sir Arthur Hurst for his systematic method of diagnosing non-organic deafness ; and I should add particularly for his aphorism that the hysterically deaf do not listen. In fact, who so deaf as those who do not wish to hear ? Indeed do we not have to ask why after a period of temporary deafness, organic in character, certain persons turn a deaf ear ? In active warfare, the unfamiliar violent explosions must necessarily produce a disturbance in nerve conductivity. Not a few but many were, in the last war, subject to these violent sensory experiences and, as we know, the majority were soon restored to normal hearing. What was the selective agent which determined the continuation of deafness or the inability to listen ? It is difficult to believe that these persons had *forgotten* how to listen. A function which is in operation so soon after birth can hardly be unlearnt in so short a time. Even the function of speech disturbed to an aphasic degree after certain cerebral injuries is rarely completely lost, for some channels of receptivity and projection are still available and symbolic activity still remains, though limited in scope. We have to assume therefore that, if unlearning has resulted, it must be central in character. But although central in character, it bears no relation to the aphasias since written language is retained, lip-reading is rapidly acquired, and spoken language also remains intact. The deafnes therefore, though central in origin, bears no relation to language in its neurological auditory aspects. Language is dependent upon auditory imagery and not only upon auditory sensations. If, therefore, the art of listening has been suspended, it must concern the process of attention. Moreover, it is legitimate to inquire what aspect of attention. Partly peripheral, for the motor reflex is lost, partly central, for under hypnosis and in sleep deafness persists. These have been my observations also in war cases. The attention—or active listening—must be lost in a selective sense, yet the patient is actively attentive to language for, as we hear, he rapidly acquires lip-reading. In other words, when confronted by a speaker in a face-to-face relationship, he is very actively attending. We must therefore conclude that the subject is somehow purposively, not purposely, rejecting all auditory experience which might come to him, particularly in a relationship which is not, as it were, face to face. The patient therefore does not wish to listen and actively rejects auditory experience.

We remarked that some only retained their deafness and therefore certain personality types, or more strictly persons in a certain mood, are prone to reject an aspect of experience—in this case auditory. In warfare to-day there is very good reason for rejecting some aspects of experience. Sights as well as sounds are nocuous and intolerable, as are certain activities, and at a higher level of the mind certain objectionable tasks and values too. In the emotional state which accompanies a bombardment there are, as we know, periods of meditation which give time, however

brief, for putting up defences against painful experience—there may be moments when flight alone will deliver the panic-stricken from a zone of danger, but the mechanism of partial dissociation is utilized in order to obliterate the world of danger, to block the channel of reception of the dangerous and the hurtful. In times of emotional distress when a man lives on an instinctual level, it is not difficult to utilize the primitive argument—I do not wish to listen—I cannot hear.

While the cases of organic deafness of the war occurred as a result of traumatic incidents causing a spontaneous loss of auditory attention, those cases I was privileged to examine were able to record a prodromal period of emotional distress. In two cases of functional deafness there was an admitted history of hyperacuity. One such soldier had the job of being at a listening post where he was expected to record and to respond to all adventitious sounds which indicated mining operations—sapping and morse-code sounds. These minute sounds got on his nerves so much that he craved for loud noises to break the painful monotony of long periods of silence. When he was blown up, he lost the sense of hearing, with a period of retrograde amnesia. In this case hypnosis was of no avail, but automatic writing by the planchette was used and recovered sufficient material to restore the amnesia to conscious awareness by way of written free associations. In the first instance, the first type of auditory stimuli of low intensity had great psychical significance with a supercharge of affective tone. This apparently produced a state of anxiety which could only be solved by some escape mechanism. The signal for discharge at the instinctual level was afforded by the episode of being blown up. In unconsciousness was found a legitimate and excusable mode of escape, and in the subsequent auditory insensibility the soldier was able to specify his rejection of the painful duties he had been obliged to perform.

In those cases which defied early attempts at cure by re-education, the psychical apparatus at greater depths became involved and the personality as a whole became eventually implicated. Predisposition to neurosis now asserted itself, and the barrier of deafness became an expression and symbol of the rejection of a dangerous external world. In my experience certain types of character only were prone to long-standing psychical deafness—the paranoid type. This type is notable for over-sensitivity, suspiciousness amounting at times to ideas of persecution. There are other forms of sensory loss met with in psychiatric practice which are not associated with paranoid trends. The blind, even in general ophthalmic practice, when blindness has become complete, are notable for an air of resignation ; they seem gladly, as it were, to accept their affliction. The sensory losses of hysterics are accepted with a strange indifference. Not so those who have lost auditory sense. The early cases of hysterical deafness do indeed betray the *belle indifférence* notable in hysteria, but the long-standing cases show irascible nature, suspicion, and some measure of persecution. We know how paranoid persons suffer auditory hallucinations which may have started by vague and meaningless eustachian explosions. But their subsequent formulation in the shape of accusatory voices and obscene remarks proves the central origin of these auditory experiences. These are images and not percepts, but their quasi-perceptual intensity blunts auditory reception of an objective kind. The inner world of delusional thinking supplies an auditory experience by projection outwards.

In the mature case, in my submission, the original hysterical loss marks the already established paranoid trends.

Here is a case from civilian practice :—

R. J. was brought up in France where with English parents and a French nurse he was bilingual. One day during a period of his parents' absence from France, he was told by his nurse in French, at the age of 7, that his mother had died in England. From that day onwards he lost the power of speaking French and of hearing French. His auditory sense for English and German is perfectly normal, but he has since lost the power of hearing French words.

There is no doubt that functional deafness is the most obstinate form of neurosis from the therapeutic point of view. Of all the sense experiences the auditory is the

most human of them all—the one most closeiy bound up with human environment and with higher aspects of the mental life. Music and speech apart from mere noise have no counterpart in the external world, and therefore for the proper understanding of functional deafness we must look for disturbances in the mental life, particularly for disturbances in human emotional relationships.

Auditory experience has very special relationships to the mental life. Unlike sight and touch, it enters very slightly into the schemata of the body image ; even our power of localizing sound is very defective. Language is the most intangible of experiences, yet both music and sound are capable of mathematical formulation. Through sound, psychical experience can be made to enjoy wide expansion and to suffer extremes of shrinking. Functional deafness is a form of psychical shrinking. The loss has little to do with hearing processes, but it is essentially bound up with emotional aspects of the personality.

Section of the History of Medicine

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Trotula and the Ladies of Salerno : A Contribution to the Knowledge of the Transition between Ancient and Mediæval Physick

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[ABRIDGED]

THE first incentive to this essay came from *Bibliotheca Osleriana* (1929), where, referring to the salernitan gynæcological treatise, entitled *De passionibus mulierum, ante, in & post partum*, usually attributed to Trotula, it is said :

> The first woman professor has been deprived of more than her chair by the unchivalrous mythoclasts of the school of Sudhoff. The Good-wife Trotula passed long ago into the fairy-tales as " Dame Trot " . . . Alas ! she too had no real existence.

Medal struck in Naples early in the nineteenth century to commemorate Trotula. The inscription says FLORVIT ANN. XI. ; the eleventh century is meant. (Photo by kind courtesy of the Boston Medical Library, U.S.A.)

This ruthless destroyer of charming legends was Charles Singer, who jointly with Dorothea Singer, in the Sudhoff Festschrift, 1924, attempted a literary reconstruction of the medical school of Salerno, the first University. The Authors suggested that the fragmentary compilations attributed to a Trotula of Salerno were in reality by a man, Trottus, but had been ascribed to a woman, because of the " peeping Tom " nature of the observations they contained, and concluded :

> The situation is not devoid of humour and thus fades into nothingness the first woman professor whose life a learned medical historian once essayed to write.

This opinion appeared in later writings, was quoted by Thorndike (1929), and then by Powicke and Emden, editors of Rashdall's *The Universities of Europe in the Middle Ages* (1936) and others besides.

Such a sharp break with cherished tradition could not remain unchallenged ; Kate Hurd Mead (1930 and 1938) argued with spirit and a wealth of quotations, that during five centuries after Trotula's death, numerous authors had accepted her existence, quoted her by name, praised her ability and that moreover her writings had been highly prized, enjoyed a wide distribution and during all this time from no source had there arisen any doubt as to her identity.

It is an invidious task to decide between these contrasting opinions, for it cannot be easy, if at all possible, to prove that a woman named Trotula practised gynæcology at Salerno ; and what is even more difficult, to obtain evidence that she wrote, or dictated, or inspired the compilation of the original text from which are derived the many extant MSS. listed under her name. What has been found feasible and is historically more essential, was to obtain an unambiguous conception of the importance and significance of *De passionibus* against the background of medical knowledge and practice of the twelfth to thirteenth centuries in Southern Italy and its consequent influence across time and land in relation to medicine.

Available " Trotula " MSS. ; Copies, Excerpts and Imitations

The earliest Trotula MSS. date from the time when in Italy and France the practice of medicine first appeared as a learned profession and universities began to train physicians and surgeons in the manner we see nearly everywhere to-day. This change in status was connected with the writings and example of the Salernitan Masters, who in their turn were influenced by personal contact with Eastern physicians. This important subject will be discussed in a later essay, but here it can be recalled that among Salernitan writings those known as *Trotula* certainly deserve particular notice. The much-quoted *Regimen Salernitanum* was, in its original form, a brief popular exposition of hygienic rules ; therapeutic medical matter was added in the fourteenth to fifteenth centuries, by authors unconnected with Salerno, for by then its glory had departed.

Trotula's treatise has been the subject of a Leipzig Dissertation by Spitzner (1921), who listed twenty-one MS. copies in various German, Belgian and French Libraries ; Cambridge and Oxford are credited each with a copy. I can enlarge this list, since four Trotula MSS. are available in Cambridge, fourteen in the Bodleian and various Colleges at Oxford, and about eight or nine are in the British Museum, while two are listed in the Hunterian Library at Glasgow. It can be assumed that some of the MS. copies originate from the Libraries at Canterbury, the Catalogue of which has been published by M. R. James (1902). A Trotula writing was also listed in the Library of Tichfield Abbey, *see* R. M. Wilson (1940). The many MSS. copies, numerous allusions in literature and repeated printings, all concur in showing that the gynæcological treatise connected with the name of Trotula was widely accepted as a guide

during four or five centuries. Moreover it can be said that it is the first writing in the Christian era which considered obstetrics from the standpoint of the medical practitioner.

Thus the preliminary examination of the MSS. available in England enabled me to express an opinion on some controversial subjects in relation to Trotula, the Ladies of Salerno and their position in the famous *Civitas Hippocratica*.

Authors discussing Trotula have usually relied on the text of printed editions, expecting that it corresponded to some early original MS. Even a cursory examination of the MSS. in England revealed that those listed under Trotula differed considerably in extent, wording, and even content. Some are brief treatises relating to gynæcological matters; others are cosmetic formularies under the title *De ornatu mulierum*; some consist of a combination of both. The Trotula in the University Library, Cambridge, is a copy of the gynæcological section of the *Thesaurus pauperum* attributed to Petrus Hispanus, a Portuguese theologian, who taught medicine at Siena, *c.* 1250, and became Pope John XXI (1276-7).

Some Trotula texts appear to have been listed under the title of *De secretis mulierum* which rightly belongs to the writing attributed to Albert Magnus (1193–1280); it contains astrology and Aristotelian disquisitions, which would not be accepted in the medical text of Trotula. No copy of Albert's *De secretis* contains a section on cosmetics, which would be foreign to the monkish trend of this writing.

The School of Sudhoff and Trotula

In a Leipzig Dissertation, Hiersemann (1921) assumed that the "Trot" MS. in the Breslau *De aegritudinum curatione* was an excerpt from a—suppositious—*Practica* by one Trottus, whose name does not appear in any Salernitan document. Though the scribe's marks such as "Trot" —tt— &c. can be variously interpreted, as a further deduction it has been concluded that this imaginary Trottus was the author of *De passionibus mulierum*. A clear distinction must be made between the author or authoress of this Salernitan treatise, who is uncertain or unknown, and the matron Trotula who: *vocata fuit quasi magistra operis*, according to most MS. This is a definite person and may even have been the matron, who, it is stated in the introduction, inspired the writing of the gynæcological treatise.

It was hoped to obtain some hint as to the authorship of the text by an examination of MSS. copies; but the one at Caius, at the point where the printed version says *compulsa*, instead employed the impersonal *me impellit*. The MS. in St. John ends with: *Factus a muliere Salernitana quae Trotula vocatur* in the same handwriting as the text. This thirteenth century view can be accepted till evidence to the contrary is forthcoming.

The attribution of the text to Eros, a freedman of the Empress Julia in the second century, appeared in the printing of 1566; it is not quite clear why this gratuitous assertion was made. Most MS. copies admit the authorship of Trotula by inference. The example of the so-called Cleopatra writing shows that dedication and authorship were not always kept separate; moreover, the Salernitan writings of Copho were often attributed to Galen.

The gynæcology and obstetrics of Trotula show some progress on contemporary practice, because of the recommendation of support of the perineum in childbirth and the primary suture of lacerations.

The professional outlook displayed in the text in relation to abortion and cognate matters is superior to that noticeable in printed copies of *Thesaurus pauperum*, the MS. of which would be approximately contemporary with Trotula. Like other

Salernitan writings, Trotula recommends numerous ineffective means and repulsive excrements, but can definitely be said to ignore magic and astrology.

The sections dealing with cosmetics have been neglected by medico-historians, but they reveal a different authorship and are especially feminine in sentiment and sensibility. It has been overlooked that here the author mentioned in the first person the prescription of a Saracen woman. There are, moreover, allusions to *Mulieres Salernitanae* who prepared aids to beauty and *Nobiles Salernitanae* who used them. All this suggests that a Trotula of Salerno could have provided material for the text of *De passionibus*.

The Women and the Ladies of Salerno

De Renzi's oft-quoted assertion that the *Mulieres Salernitanae* taught medicine in the School of Salerno seems based on Mazza (1681) who, writing some four or five centuries after the apogee of the *Civitas Hippocratica*, rather confused the authorship or the alleged authorship of medical writings with the position of an academic teacher. Moreover, De Renzi accepted the reference to a wise matron of Salerno by Orderic Vitalis as a definite mention of Trotula ; a somewhat light-hearted assumption. The existence of the School or College of Salerno in the eleventh century is uncertain ; the activity of the Masters was apparently restricted to medical practice and the issuing of medical excerpts, and if it could be proved that Trotula was the author of *De passionibus mulierum*, then she might well rank as a teacher or instructress ; it is, however, difficult to accept her as the first Woman Professor. Instead there is documentary proof that Constanza Calenda of Salerno lectured on medicine *ex cathedra* some time during the reign of Giovanna I of Anjou (1326–82) in the University of Naples.

The reference to Trotula in the Prologue to the *Wife of Bath* tale may be connected with the existence of several copies of Trotula which were present in the Library at Canterbury in the fourteenth century ; these were probably known to Chaucer only by their title, which may have given an erroneous conception of their serious medical contents.

The study of MS. copies in England failed to confirm that Trotula of Salerno actually wrote or compiled *De passionibus mulierum*, but since scribes in the thirteenth to fourteenth centuries assumed that she did, one may accept this traditional view, till proof to the contrary becomes available. There is no sound evidence that Salernitan women practised or taught medicine as *Magistræ* ; what Gilles de Corbeil described were the manipulations of home treatment of different ailments ; it must be remarked that such treatment was given independently of the direction of any *Magister*. Indeed in *De passionibus* it was expressly stated that *Trotula . . . vocata fuit quasi magistra*, just as if she were a Master of Medicine. Writings ascribed to other Salernitan women have not yet been traced, but there are the remarkable literary efforts of St. Hildegard of Bingen (1098–1180), together with the *Hortus deliciarum* of the nun Herrad von Landsperg (d. 1187) ; thus any writings of Salernitan women that may be discovered would not be unique. Whoever may have been the actual composer of *De passionibus mulierum*, the treatise itself can be considered in the light of a notable achievement at the time, for it taught the professional handling of gynæcological and obstetrical conditions in a manner not only more enlightened than was usual at that time, but as part of a *Magister's* practice. The section dealing with cosmetics may well have been composed by a woman, though physicians from Soranus to Mayerne (d. 1655) have prescribed aids to beauty.

Therefore judged by any criterion or tried by any suitable test, the Trotula text proves to be one of the most significant treatises issued by Salernitans.

The Masters of Salerno and the Origin of the Medical Profession in Western Europe.[1]

It is usually accepted that a broad stream of Hippocratic medicine can be traced from classical times to the present. Hippocrates was mainly concerned with the observation of symptoms for the purpose of prognosis ; seven centuries later, Galen made diagnosis subservient to therapy. During the following nine centuries, the Hippocratic stream became a mere trickle, just recognizable in the writings of philosophers like Hrabanus. In Western Europe in the ninth century the practitioner of medicine, when not a monk, was a *medicus*, who employed spells and charms and could scarcely read or write. Not so in the East, where physicians and surgeons were trained by learned teachers. At the time of the first Crusade the Masters of Salerno first arose, adopted the title *Magister* like that of expounders of the law, and taught by means of the excerpts and compilations of Moslem and Hebrew writers by Constantine of Monte Cassino—d. *ca.* 1087. The Salernitans established by example and precept that the practitioner of medicine should be a learned person, not only a skilled craftsman. They concentrated on the treatment of symptoms, made a timid attempt to learn anatomy and, what is particularly remarkable for their time and locality, avoided magical formulæ or miraculous faith-cures. It can be surmised that they modelled themselves on the practice of Moslem and Hebrew physicians. The productive literary activity of the Masters stopped with the sack of Salerno in 1196, but the famous edict of Frederick II regulating the practice of medicine was issued in 1240 ; by then a " College " had been formed. The *Regimen Salernitanum* in its original form was not particularly medically important ; when it became popular, it was altered by several copyists ; the significant Salernitan writings are *Copho*, *Antidotarium*, *Trotula*, *Rolandina*, and *De Adventu*. The essential achievement of the Salernitans was the advancement of medical practice on those professional lines it has preserved to the present day.

The Medical and Alkemikal Writings Attributed to Queen Cleopatra.[1]

It can be objected that it does not really matter whether Queen Cleopatra was in any way connected with the writings attributed to her. Since some are palpably pseudo-epigraphic and the general verdict is that all are forgeries, there is little purpose in trying to ascertain how and when these writings were attributed to the glamorous Queen of Egypt.

Still, it may be said that a clear conception of the development of medical knowledge through the centuries cannot be obtained by restricting study to a few acknowledged classical authors without also considering the many minor writings which must have influenced medical practice during the centuries. For example, the excellent medical works of Celsus remained unknown for eleven centuries, whilst many inferior writings enjoyed great popularity, were copied and re-copied times without number, and medical practice followed scarcely recorded doctrines and methods.

For these reasons the origin of the gynæcological writings attributed to Cleopatra has been examined and it has been found that in the form in which they were printed in the *Gynaecia* of Wolf, 1566, they are mainly excerpts from the writings of Soranus, *c.* A.D. 80–90. The source of the writings of Mustio-Moskion is the same, hence the resemblance with the Cleopatra MSS., though certain differences are noticeable. The Alkemy writings were, in all probability, not composed before the third century, while those in cosmetics may well have originally been contemporary with Queen Cleopatra or even earlier.

It is hoped to publish these essays *in extenso*. Limitation of space precludes me from adding a list of references and works consulted ; they can, however, be easily traced by students of the subject. Sarton's *Introduction to the History of Science* (Balt., 1927) contains an up-to-date consideration of Salernitan authors and bibliography of original writings.

I have received kind help in these investigations from many friends, but I may be allowed to mention Dr. Charles Singer, whose advice, criticism, and sustained interest has proved most encouraging.

[1] Abstract of paper read by Dr. Bayon at the meeting of the Section held June 5, 1940.

Section of Therapeutics and Pharmacology

President—Sir WILLIAM WILLCOX, K.C.I.E., C.B., C.M.G., M.D., F.R.C.P.Lond.

[*March* 12, 1940]

DISCUSSION ON THE INDICATIONS FOR OXYGEN THERAPY AND METHODS OF ADMINISTRATION

Professor B. A. McSwiney pointed out that about 360 c.c. of the 500 c.c. of air drawn in at an average breath reach the alveoli, 140 c.c. being required to fill the air tubes (dead space air). The alveolar air must contain therefore more carbon-dioxide and less oxygen than the mixed expired air which consists of alveolar air plus unchanged dead-space air which is expelled first on expiration.

The composition of the alveolar air in resting subjects at normal atmospheric pressure is nearly constant. The alveolar air contains about 14% O_2 and 5·6% CO_2.

The air in the alveoli is separated from the blood in the capillaries by the walls of the pulmonary epithelium and the endothelium of the capillary wall. The exchange of gases takes place by a process of simple diffusion depending on the partial pressure of the gases, the character of the membrane, and the solubility of the gases.

Oxygen in the alveolar air is at a partial pressure of 100 mm.Hg, while that in the venous blood is at 40 mm.Hg, consequently oxygen passes from the alveoli to the blood. The carbon-dioxide in the venous blood is at a higher tension than the alveolar carbon-dioxide, hence carbon-dioxide diffuses into the alveoli of the lungs.

The full oxygen combining power of hæmoglobin in 100 c.c. of blood is 20 c.c. As the blood is normally 95% saturated, 100 c.c. of arterial blood contains 19 c.c. of oxygen combined with hæmoglobin and 0·3 c.c. in solution, a total of 19·3 c.c. of oxygen.

Oxygen want in the body from any cause is termed anoxia. Four types are described: (*a*) Anoxic anoxia; (*b*) anæmic anoxia; (*c*) stagnant anoxia; (*d*) histotoxic anoxia.

In the first, the type seen in lung diseases, congenital heart diseases and at high altitudes, the hæmoglobin is not saturated to the normal extent. This may be due to alteration in the pulmonary epithelium or to a decrease in the partial pressure of oxygen. In the second type, the oxygen capacity of the blood is reduced due to a reduction in hæmoglobin. In stagnant anoxia the oxygen content of the arterial blood is normal, but a large part of the oxygen supply is delivered under low pressure since the blood gives up a large proportion of its oxygen due to a slow blood flow through the capillaries. In the fourth type oxygen cannot be taken up and used by the cells.

Anoxic anoxia may be benefited by oxygen therapy. By increasing the percentage of oxygen in the alveolar air the partial pressure of the gas will be raised and the oxygen content of the blood increased.

Recent work by Boothby and his co-workers at the Mayo Clinic suggests that the administration of oxygen in high concentrations may be of benefit in other types of anoxia.

Three different methods of oxygen administration for use in adults and older children were described: (1) Nasal catheter; (2) nasal tubes; (3) masks.

It was shown that the efficiency of nasal catheters and nasal tubes was similar, but that nasal tubes were more comfortable. With a flow of 4 litres a minute 33% of oxygen may be obtained in the alveolar air.

The apparatus designed by Boothby, Lovelace and Bulbulian (1938) has many advantages. In the first place by its use any desired concentration of oxygen between that in air and practically pure oxygen can be administered; secondly, the apparatus is comfortable and can be worn for long periods; thirdly, the mask fits over the nose so that the mouth is free for feeding and talking; finally, the apparatus is mechanically simple and easy to operate. With the B-L-B. inhalation apparatus it is possible to obtain alveolar oxygen concentrations ranging from 45 to 90%.

The difficulty of operating oxygen tents was discussed, and it was considered that these were only of value in institutions where facilities were available for maintaining a proper service.

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Professor R. V. Christie: In general, the onset of cyanosis is the most important indication for oxygen therapy, but unfortunately while the relief of cyanosis with oxygen may be spectacular in some cases, it is imperceptible in others. It is important that the clinician should be able to recognize those cases likely to benefit from oxygen and those who are not, but this will only be possible if he appreciates the symptoms of anoxæmia and its dangers, and understands certain simple principles on which oxygen therapy is based.

The first principle concerns the dangers of oxygen lack. The more harmful anoxæmia is shown to be, the more important it is that oxygen should be given early and efficiently. Anoxæmia, if very severe, may result in permanent damage to the nervous system but, except in carbon-monoxide poisoning, this is rarely seen clinically. Much more common and more important is the effect of oxygen lack on the heart. There is ample evidence that the degree of anoxæmia often seen in bronchopneumonia, phosgene poisoning, or acute heart failure, is sufficient to embarrass the heart of a healthy individual, and in these conditions relief of anoxæmia by means of oxygen may be a life-saving procedure. Since the cardiovascular system is the first to suffer, any assessment of the effects of oxygen therapy should be based partly on careful observation of the pulse: a reduction in the rate of the heart-beat or an improvement in the quality of the pulse is an important indication of successful treatment.

The second principle is that hæmoglobin is almost completely saturated with oxygen when exposed to ordinary inspired air, and therefore the administration of oxygen to a healthy person does little to increase the quantity of oxygen taken up by the blood. In an individual whose arterial blood is fully oxygenated in the lungs but whose hands are blue because they are cold, or who has widespread cyanosis due to a sluggish peripheral circulation, the administration of oxygen cannot be expected to relieve the cyanosis. Again, when the blood passing through certain parts of the lung is not aerated, the addition of oxygen to the air in the healthy parts of the lung will have but little compensatory effect. For instance, in a case of lobar pneumonia where the left lung is consolidated and the right unaffected, any cyanosis that is present will be due to the flow of blood through the consolidated and unaerated left lung. If oxygen is given it can only reach the blood passing through the solid left lung by the very slow process of diffusion, and as the blood flowing through the healthy right lung is already fully aerated, no amount of oxygen will supersaturate it. On theoretical grounds therefore little relief of cyanosis can be expected from oxygen

therapy where the anoxæmia is due to the flow of blood through consolidated lung, and the same is true of other conditions, such as pneumothorax or massive collapse of the lungs, where ventilation in parts of the lung is completely obliterated. Fortunately anoxæmia is seldom severe in these cases, since in the airless parts of the lung the pulmonary circulation rapidly diminishes and in time is almost obliterated. This latter phenomenon is well illustrated in the case of artificial pneumothorax where, even with extensive collapse, cyanosis is seldom seen.

In bronchopneumonia or acute pulmonary œdema the situation is entirely different. Here the patches of consolidation are small or minute, and it is a deficiency of ventilation which causes anoxæmia. The quantity of air which enters the affected areas is insufficient to oxygenate the blood passing through them and this deficiency can be effectively overcome by enriching the inspired air with oxygen. The same is true of other conditions such as asthma or emphysema where cyanosis is due to a generalized underventilation of the blood in the lungs. Oxygen, if properly given, should compensate for underventilation and should efficiently relieve anoxæmia.

These generalizations can be restated in terms of physical signs; where moist sounds are plentiful and widespread, anoxæmia is often severe and oxygen, if properly given, should relieve cyanosis, but where added sounds are few or absent and bronchial breathing or suppression of breath sounds are conspicuous, oxygen is usually of little benefit.

The third principle is that lack of oxygen rarely, if ever, is the direct cause of dyspnœa. While the majority of patients who are ill and who complain of dyspnœa are also cyanosed, this by no means proves that the one is the cause of the other. Cyanosis is frequently said to be the cause of dyspnœa, not because of any proved relationship, but because it seems reasonable to suppose that the impaired respiratory function should be responsible for the respiratory symptoms. Nevertheless there is no foundation for such a supposition. In uncomplicated anoxæmia, such as is seen in carbon monoxide poisoning or when flying at very high altitudes, dyspnœa comparable to that in pneumonia or cardiac failure is never observed, although the pilot may be incapacitated by oxygen want. Anoxæmia by its action on the carotid sinus or gland may cause slight hyperventilation but not respiratory distress. It is true that even mild exercise at high altitudes may cause dyspnœa, but the evidence available suggests that this is due to cardiac embarrassment and pulmonary congestion rather than to any direct chemical stimulation. The practical bearing of these observations is that in pneumonia and in other conditions where dyspnœa is primarily due to an inflammatory lesion in the lung and not to cardiac failure, the relief of anoxæmia cannot be expected to produce any reduction in respiratory rate. For this reason, the use of the symptom dyspnœa as an indication for oxygen therapy, or as a criterion of the efficacy of oxygen, is fallacious in most cases.

The fourth principle is that if oxygen is to be given at all, it should be given more or less continuously. The administration of oxygen for ten minutes in every two hours to a patient who requires oxygen can only mean that he is denied the relief of anoxæmia for nine-tenths of the time.

These are the general principles which decide the therapeutic indications for oxygen therapy, and their application to disease is not difficult.

In severe *bronchopneumonia, acute pulmonary œdema*, and *poisoning with the lung-irritant gases*, there is exudate scattered throughout the lungs, and anoxæmia, which is frequently severe, can be relieved by oxygen. In this type of case, the early and efficient administration of oxygen may be a life-saving procedure.

In *lobar pneumonia*, the therapeutic value of oxygen is in considerable dispute. There is no good evidence that oxygen therapy lowers the mortality rate or shortens the course of the disease, and even the relief of cyanosis is often imperceptible. Where cyanosis is due to outspoken consolidation little relief from oxygen is to be expected, but in the majority of patients with lobar pneumonia there are some areas

where consolidation is incomplete, and in these areas the administration of oxygen may be of some value. In other words, it is often impossible to state with certainty that oxygen will be of no value in a case of lobar pneumonia. It is usually better therefore to give oxygen a trial if the patient is cyanosed; if the patient dislikes this procedure or if it prevents sleep, it should be discontinued for a while and only given again if cyanosis increases. Fortunately, anoxæmia is seldom severe in lobar pneumonia.

After a large *pneumothorax*, *hydrothorax*, or *hæmothorax*, cyanosis is usually transient. If it persists, removal of air or fluid from the pleural cavity is indicated, rather than the administration of oxygen.

Oxygen is of little or no value in the treatment of long-standing cyanosis such as is seen in *chronic heart failure* or *emphysema*, and should be reserved for the acute emergencies that frequently occur.

While the onset of cyanosis is the most important indication for oxygen therapy, there are three groups of clinical conditions without cyanosis in which the administration of oxygen is claimed to be beneficial.

The *first group* is where cyanosis is masked by anæmia. The greater the degree of anæmia the greater may be the anoxæmia without cyanosis, until, when the hæmoglobin falls to 30% the patient cannot be cyanosed although he may be suffering from a very dangerous degree of oxygen lack which can be relieved, partly at least, by oxygen. This clinical picture of anæmia and anoxæmia without cyanosis is uncommon except after operations on the lungs or wounds of the chest, but in these cases the administration of oxygen may be of value although cyanosis is not demonstrable.

The *second group* concerns a recent innovation in oxygen therapy. Where oxygen lack is due to a sluggish peripheral circulation and not to any deficiency of oxygen in the hæmoglobin it is possible to increase the amount of the gas in solution in the plasma by the administration of 100% oxygen. This increase is small, and the administration of pure oxygen requires special apparatus, but in view of results which have been obtained it seems possible that oxygen is of value in the treatment of shock.

The *third and last group* concerns another recent innovation in oxygen therapy. It is claimed that the inhalation of pure oxygen will facilitate the absorption of any collection of gas which is trapped in the body. The administration of oxygen in high concentrations is therefore advised in conditions such as air embolism, surgical emphysema, and severe abdominal distension.

Dr. J. McMichael: *Practical experience with the B-L-B mask.*—My experience of the B-L-B mask has only extended over six weeks, but during this time we have had a large number of cases of bronchopneumonia through the acute medical wards at Hammersmith Hospital. With two masks in use we have been able to treat the most severe cases only, and in every case we administered 100% oxygen from the beginning, and only reduced the concentration as the patients improved.

(1) *Efficiency.*—The high degree of efficiency of the method is beyond doubt. One has only to see the disappearance of a mauve cyanosis and its replacement by a healthy salmon-pink colour of the skin to appreciate this. Even in the most severe cases it was invariably possible to bring about a decided improvement in colour. One apparently moribund patient with extensive bilateral bronchopneumonia, with exudation extending up towards the clavicles, improved immediately in colour and was maintained in a good state as regards tissue oxygenation for three days before he ultimately died of the effects of infection and sepsis.

(2) *Technique of use.*—While the mask is highly efficient and simple, it requires watching.

(*a*) *The regulation of oxygen flow.*—It is stated that so long as the bag is rising and falling with respiration all is well and there is no need for a flow meter. My experience

is that without a flow meter serious difficulties and even dangers may occur. In one patient who was admitted unconscious with extensive bronchopneumonia and severe cyanosis the mask was applied and the oxygen cylinder turned on. The bag expanded and deflated with each respiration, but within a short time there was no improvement in the cyanosis and the patient had a convulsion. In error, an empty oxygen cylinder had been used, and the movements of the bag simply indicated re-breathing. This mistake is of course more likely to occur as a cylinder is running out than at the beginning, but it must be kept in mind. Some form of simple flow meter is undoubtedly essential, and a simple device is all that is needed for this purpose, together with a pressure gauge on the oxygen cylinder to indicate the oxygen content.

(*b*) *A flow meter* has further advantages in that there need be no wastage of oxygen. In many cases of severe cyanosis there seems to be considerable depression of respiration, and full benefits of high oxygen percentages may be achieved with an oxygen flow somewhat less than that recommended in the instructions with the mask.

THE B-L-B INHALATION APPARATUS.

(Block kindly lent by Messrs. A. Charles King, Ltd., 33, Devonshire Street, W.1.)

(3) *Toleration.*—All patients in real need of oxygen have tolerated the mask well. One or two restless and distressed cardiac patients have discarded the mask after short periods, but in these the indications for oxygen therapy were less clear and the benefits much less obvious. The mask allows complete freedom for fluid feeding of the sick patient and does not in any way hinder expectoration.

We have not encountered any instances of severe nasal obstruction to limit the use of the mask. An open mouth certainly diminished the benefits to be obtained. In some seriously ill, cyanotic patients, the jaw drops and is difficult to close. In such patients we have been able to obtain full benefits of the mask by placing a napkin over the mouth. It has been our experience, however, that these patients have invariably died. The wide-open mouth is a bad prognostic sign.

(4) *Circulatory effects.*—In cyanotic patients to whom the oxygen is given an asphyxial rise of blood-pressure may be lowered. We have observed this several

times. In itself this must considerably relieve the circulation, and it is often of diagnostic aid in determining the cause of pulmonary exudation.

The effect on the electrocardiogram is less obvious. In one severely cyanotic case with slight S–T depression no change resulted from oxygen administration.

(5) *Indications other than pulmonary anoxia.*—We have not yet had an opportunity of giving oxygen in shocked patients. One patient with a mixed infection type of pneumonia developed severe tympanites; this failed to respond to turpentine enemata, pituitrin, and other better-known methods. She was given oxygen, and within twelve hours was much more comfortable and the abdomen had completely deflated in thirty-six hours. The benefits achieved by washing out inert gases are certainly striking and give this new mask a further field of practical use.

The mask constitutes a most valuable addition to our therapeutic armamentarium.

Mr. J. E. H. Roberts, after congratulating the openers on their admirable papers, said that from the point of view of the surgeon there were two types of patient in whom cyanosis was not present although they were anoxæmic. One was the patient who was anæmic from the loss of blood during an operation or from wounds, and the other was the anæmic patient in whom it was impossible by blood transfusion to raise the hæmoglobin to as high as 80% pre-operatively. Both these patients might need oxygen although cyanosis was not seen.

Then there was the patient who had what might be called " psychical dyspnœa " post-operatively in whom there was probably inco-ordination between the diaphragmatic and costal movements. These patients were pacified and settled down rapidly when given oxygen.

Deficient ventilation of the lung from interference with the movements of respiration such as occurred in thoracoplasty operations was also an indication for oxygen therapy, as was deficient ventilation from stricture of the trachea, for instance by a large goitre.

Section of Comparative Medicine

President—C. H. Andrewes, M.D., F.R.S.

[*April* 24, 1940]

Induction of Fertility by the Injection of Gonadotrophic Preparations

By A. S. Parkes, F.R.S., and John Hammond, F.R.S.

I

Dr. A. S. Parkes (*Medical Research Council*).—I propose to discuss briefly the biological basis of the work carried out during the last eighteen months on the induction of increased fertility in sheep. Dr. Hammond will deal with its possible application to agricultural practice.

Removal of the anterior pituitary body from an animal causes cessation of reproductive activity. Conversely, if an extract of the anterior lobe is injected into an hypophysectomized or otherwise reproductively quiescent animal then the gonad, particularly the ovary, undergoes stimulation and in many cases ovulation and the formation of corpora lutea results.

It might be supposed that wide possibilities of increasing the fertility of animals were thus opened up, either of increasing the number of ova shed during the normal ovulation period, or of stimulating the quiescent animal. Unfortunately, many difficulties have been encountered in the practical use of gonadotrophic extracts for increasing fertility, and up till recently the results have not been very promising.

The normal ovarian cycle consists of two phases: the maturation and rupture of one or more graafian follicles, and the subsequent development of a corresponding number of corpora lutea. The first of these phases is correlated with the appearance of willingness to accept the male, and the second with the changes characteristic of early pregnancy. If a crude extract of anterior lobe is injected, in most cases a mixture of these two ovarian phases is produced, and generally the result is chaotic ovarian activity not at all like the orderly changes which normally take place. From the results obtained it seems likely that not less than two anterior pituitary substances are present in the anterior pituitary, one concerned with the production of ripe follicles (follicle-stimulating hormone) and the other with the development of the corpus luteum (luteinizing hormone). In crude extracts both of these two substances occur, in varying proportions, and injection of such an extract stimulates the ovary to undergo two phases of development at once, their relative intensity depending on the proportion of the two substances present.

Qualitative properties of the more important gonadotrophic extracts.—Anterior pituitary extracts are obtained most easily from the anterior lobes of horse, sheep, pig, and ox. The anterior lobe of the ox contains little gonadotrophic material and

that present is largely luteinizing hormone. Sheep and pig anterior lobes contain appreciable amounts of material and from them quite active extracts can be obtained. Unfortunately the luteinizing hormone appears to preponderate, and it is difficult to produce any orderly stimulation of the ovary of hypophysectomized animals with crude extracts from these sources. On the other hand the extracts of horse pituitary are extremely active and contain a preponderance of follicle-stimulating material; the changes produced by the use of crude horse pituitary extracts resemble those seen in the normal ovary.

Extracts of blood and urine.—Two other well-known gonadotrophic preparations are obtained from species in which the body fluids during pregnancy contain very large amounts of gonadotrophic material. The blood-serum of the pregnant mare, particularly during the third month of pregnancy, contains relatively enormous amounts of gonadotrophic material. In women, the urine during pregnancy contains very large amounts of a gonadotrophic substance which is very different in biological action from that found in the serum of the pregnant mare. Whether or not the substances present in the body fluids during pregnancy are elaborated by the pituitary gland is not clear. They may originate in the placenta or in the pregnant uterus.

Determination of qualitative properties of extracts.—If the qualitative activity of gonadotrophic extracts is tested on an intact animal there is the theoretical possibility that the animal's own pituitary may contribute to the effect produced, even though the test animal is reproductively quiescent at the time. In practice it has been shown that the effect of the injection of a gonadotrophic extract may be greatly modified by the presence of the animal's own pituitary, which, moreover, appears to be stimulated by the changes artificially induced in the ovary, and contributes to the effect produced.

The degree to which the animal's own pituitary affects the response differs in different species, but it appears to be maximal in the immature female rat, the most commonly used test animal.

Experiments on sheep.—These general principles are well illustrated by the work on sheep, and our own investigations have been carried out with horse pituitary extract, which seems to have particularly suitable qualitative properties.

The first experiments, consisting of injecting out-of-season ewes shortly before slaughter, showed that it was possible to produce ovulation during anœstrus by the injection of horse pituitary extract. The number of follicles ovulated was one to three, i.e. normal for sheep. Later experiments showed that treatment of sheep during the last three or four days of a normal œstrous cycle caused super-ovulation at the next œstrus. Injection at any other time of the cycle or during pregnancy did not cause ovulation, but merely enlargement of follicles.

Flock experiments.—These short-term experiments were followed by work on a normal flock, which revealed several points of importance. If ovulation is induced in an out-of-season ewe it is not usually accompanied by full œstrus, i.e. by willingness to mate. It may be necessary to give a second injection after an interval of sixteen to seventeen days and to cause, therefore, what amounts to one complete artificial cycle, before mating will take place.

Working along these lines on Dr. Hammond's experimental flock in Cambridge last year seven ewes were induced to take the ram out of season, and of these four ultimately produced lambs, the total being seven, giving an average of one lamb per ewe.

II

Dr. John Hammond (*School of Agriculture, Cambridge University*).—There would seem to be a wide application for this hormone in the practical problems of sheep production. The chief applications appear to be as follows:—

(*a*) *To reinforce œstrus in ewe lambs, breeding during their first year.*—Breeders have

frequently hesitated to breed from ewe lambs because of the detrimental effect on the ewe herself and because the lamb is often small and weak at birth and the ewe has but little milk. It has been found that the feeding of the ewe during the latter part of pregnancy has a marked effect on birth-weight and milk secretion. By lambing ewe lambs later in the season, about a month after the grass has begun to grow in the spring, these bad effects may be overcome. One good effect of lambing from ewe lambs is that they appear to make better mothers if they produce lambs early in life.

On the average only about 70% of ewe lambs put to the ram normally become pregnant; this, however, varies greatly in different flocks and seasons. Tests have been made this last breeding season to find out whether injection at the time they are on heat will increase the number of conceptions; no results are yet available. In mating up ewe lambs during December and January a certain percentage fail to accept the ram; these can be injected, as for anœstrous ewes (*see below*), and many have been served during this last season.

(*b*) *To increase the fertility of normal matings.*—Many flocks, especially in certain breeds, give a lower lambing percentage than the optimum, and if this could be increased to about 175–200% it would raise the efficiency of lamb production.

By making the injection a few days before the onset of œstrus, the corpus luteum apparently inhibits ovulation and ripening follicles bank up in the ovary so that when the corpus luteum atrophies and heat appears a large number of follicles are ripe and ovulate. After injections of 50 mgm. horse pituitary extract frequently seven to nine ova are shed, and cases have been obtained in which seven fertilized eggs have been recovered from the tubes and five embryos taken from the uterus at about half-term.

Whether it will be possible by regulating the dose to ensure that two follicles only will ovulate has yet to be determined, but it seems likely for there is a marked effect of dose on the number of follicles which ripen in anœstrous ewes.

(*c*) *To breed from barren and lost-lamb ewes during the non-breeding season.*—The ewe has a well-marked breeding season which coincides with the short-day period of the year. The exact duration has not yet been worked out for the different breeds, but with Suffolk × Border Leicester-Cheviots it begins each year about the end of August or beginning of September and ends about the middle of March to the first week in April. There is considerable individual variation, however, and some ewes go into anœstrus as early as the middle of January; ewe lambs especially tend to go into anœstrus early.

The number of barren ewes and lost-lamb ewes is considerable, and at present no return, except a wool clip, can be obtained from these for a whole year. If these could be made to breed after the lambing had finished, a crop of lambs could be obtained in the autumn; thus, by mating after lambing was over in April they would lamb in September.

By injecting 50 mgm. of horse pituitary practically 100% of such barren or lost-lamb ewes can be made to ovulate in the anœstrous season but no œstrus occurs. An ovulation without an œstrus normally occurs before the onset of the breeding season in sheep, and it is not until the second ovulation that œstrus appears. It seems possible that if the ripening and rupture of the follicle is too rapid, as occurs when no corpus luteum is present in the ovary, time is not allowed for the symptoms of heat to develop. Whatever the explanation, the fact remains that by giving a second injection at about fifteen to seventeen days after the first, the normal duration of the cycle in sheep, both ovulation and œstrus are caused, and mating results in pregnancy. The exact time at which this second injection should be made has not yet been worked out for different circumstances such as breed, time of year, &c.

(*d*) *To obtain two crops of lambs in one year.*—In order to do this the ewes have to be mated while they are still suckling. This is at present being done in some Dorset

Horn flocks, a breed which has a much longer breeding season than other British breeds. From work this season it has been found that ewes suckling lambs can be brought into œstrus by the same method as adopted for other anœstrous ewes, although the best interval for the second injection is not yet known. The best interval between lambing and the first injection too has not been determined, although from a practical point of view it would appear that ewes suckling single lambs born early in the season form the most promising material.

(*e*) ***To speed up ewes coming to the ram at the beginning of the breeding season.***—In breeds, such as the Dorset Horn, which cater for the early fat lamb trade, there is often difficulty in getting the ewes to come on œstrus together early in the season, and the lambing is consequently spread out over many weeks. Horse pituitary should be useful in this case, but the details of the method to be employed have yet to be worked out.

In conclusion we have the impression from this season's work that the condition of the ewe may have an effect on the ease with which œstrus is induced in the anœstrous season by injection of the hormone. This seems to fit in with the known fact that flushing or extra feeding of the sheep before the tupping season increases the fertility of flocks. It may be that the hormone is dependent for its action in producing œstrus on some nutritive substance.

Section of Pathology

President—G. W. Goodhart, M.D.

[*March* 19, 1940]

DISCUSSION ON THE EFFECT OF ANTISEPTICS ON WOUNDS

Professor Alexander Fleming : Almost all chemicals, even sodium chloride, are antiseptic if used in sufficient concentration, but it is only those which have an especial power of inhibiting bacterial growth which are classed as antiseptics. There is a great variety of chemicals which fall into this category, and which have been, or are, used in surgery as antiseptics.

Seeing that the definition of an antiseptic is a chemical which will inhibit the growth of bacteria, it is remarkable that after the best part of 100 years of the study of antiseptics the tests which are commonly quoted by the manufacturers of these chemicals relate only to their power to *kill* bacteria, not to inhibit them. This power of killing bacteria in the conditions of these tests has little or no relation to the usefulness of antiseptics in a wound, septic or otherwise.

It is possible that it is because of these tests that in the consideration of local antiseptics, as well as in the study of chemotherapeutic drugs, far too much attention has been paid to the bactericidal power of the chemical, and far too little to the bacteriostatic power. It would be better if, in a consideration of chemicals for use in septic wounds, the bactericidal power were neglected, and the bacteriostatic power were accepted as a criterion. The literature on the sulphonamide drugs is a good example of how the wells of knowledge may be muddied by attempts to show that the action of these drugs was bactericidal, when their beneficial action could easily be accounted for by a consideration of the bacteriostatic power. The natural defensive mechanism of the human body against the common infections is very considerable, and is the most important antiseptic in contaminated wounds. If the scales are weighted against it by inefficient surgery then it appears to be a poor thing. But it is quite easy to weight the scales against chemical antiseptics, and to make it appear that the natural defences are far more potent than are the chemicals commonly used as antiseptics. The following experiment (Fleming, 1928) illustrates this. An ordinary nutrient agar culture plate was taken, and a series of holes were punched in it with a cork borer. Into each of these were placed discs of filter paper which had been soaked in the following substances : (1) Iodine, 1 : 100. (2) Mercurochrome, 1 : 100. (3) Mercuric chloride, 1 : 1,000. (4) Carbolic acid, 1 : 20. (5) Acriflavine, 1 : 1,000. (6) Gentian violet, 1 : 100. (7) Nasal mucus. (8) Tears.

The holes were then filled up with agar, and when that had set the whole surface of the culture plate was thickly planted with a strongly growing coccus, *M. lysodeikticus*, which is specially sensitive to the lysozyme of human secretions. After incubation it was found that there was a large zone of inhibition around the tears and nasal mucus, while over all the chemical antiseptics there was a copious growth of bacteria.

In the conditions of this experiment, therefore, the natural antiseptics, nasal mucus and tears, appeared to be much more potent than carbolic acid, mercuric chloride, mercurochrome, iodine, acriflavine, and gentian violet.

It is essential to scrutinize carefully the conditions of any test of the power of antiseptics for use in the human body.

Antiseptic Action

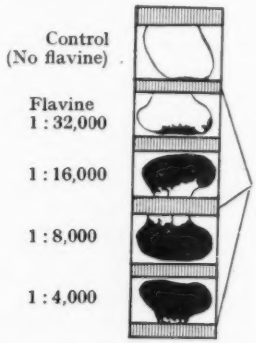
Specificity.—Some chemicals such as carbolic acid act more or less equally on all bacteria, while others, such as gentian violet and some others of the antiseptic dyes, have a specific action on some species only. It seems obvious that, other things being equal, a non-specific chemical which acted on all bacteria would be the most

valuable in a septic or contaminated wound, although it would be quite reasonable to use, if such were available, a chemical which had a powerful specific action on the streptococcus or the gas gangrene bacilli, as these organisms are a special danger in the contaminated war wound.

Quenching by albuminous or cellular media.—Some chemicals have a potent antiseptic action in a non-albuminous medium, such as nutrient broth, but when acting in serum are much less powerful, and still less so in blood or pus. A very good example is mercuric chloride, which inhibits staphylococcus as follows: In broth 1 : 500,000; in serum 1 : 30,000; in blood 1 : 2,000.

Some, such as carbolic acid, are of approximately equal potency in broth, serum, or blood.

Acriflavine has at least as powerful an antibacterial action in serum as in a non-albuminous fluid. Its potency is, however, decreased in a cellular fluid, such as pus or blood.



Imperfectly vaselined paper strips which are wetted by the blood-acriflavine mixtures. Acriflavine absorbed by paper, allowing *B. coli* to grow and hæmolyse blood. Black areas represent unhæmolysed blood. Clear areas represent blood hæmolysed by growth of *B. coli*.

FIG. 1.—Affinity of flavine for paper and for bacteria. Hæmolytic *B. coli* in human blood.

In the last war possibly the most popular antiseptic for use in septic wounds was Dakin's solution (sodium hypochlorite), especially when it was used by Carrel's method of instillation into the wound through a manifold of tubes once every two hours. I have made observations (1919) as to how long Dakin's fluid maintains its antiseptic power in a septic wound. A cup-shaped wound was chosen into which a measured volume of fluid could be introduced and removed. When Dakin's fluid was introduced and removed after ten minutes, it was found on testing the available chlorine that this had been reduced to a point below that which was antiseptic in serum. If the fluid was kept agitated during its sojourn in the wound the strength was reduced below the antiseptic level in five minutes.

Therefore, in Carrel's method, which was generally regarded as the most successful "antiseptic" treatment in the Great War, there was an antiseptic in the wound for, at the most, ten minutes out of every two hours.

In connexion with the antiseptic dyes, also, the affinity of these for the tissues and dressings has to be considered. I have, over twenty years ago, published some experiments on this point. If a piece of gauze is saturated with flavine, 1 : 1,000, and the fluid is then squeezed out, the concentration of flavine in the extruded fluid is about 1 : 5,000, showing that about 80% of the flavine has been immediately absorbed by the gauze. A very simple experiment shows the great affinity of antiseptic dyes, such as gentian violet or acriflavine, for cotton-wool. A test tube is half filled with a solution of one of these dyes, and then a plug of absorbent cotton-wool is slowly pushed down into the fluid so that the fluid has to percolate through the plug. The whole of the dye is retained on the cotton-wool, and only water passes through. It might be said, however, that this has really no bearing on the relative

affinity of the dye for the dressing and for bacteria. I have, however, an experiment which has a direct bearing on this subject.

Blood suitably infected with a hæmolytic *B. coli* was mixed with various dilutions of acriflavine, and placed in slide cells in which the paper partitions had been insufficiently vaselined, so that portions were wetted with the blood-acriflavine mixtures. The results are shown in fig. 1, and it will be seen that where the blood wetted the paper, enough of the antiseptic had been removed by the paper to allow the bacteria to grow out and produce hæmolysis in concentrations of acriflavine which would otherwise have produced complete bacteriostasis.

Similar results were obtained with gentian violet.

These experiments show that paper has such an affinity for these antiseptic dyes that it will successfully compete with bacteria for the dyestuff, and render it inactive as an antibacterial agent. This affinity of dyes for dressings and other things must be taken into account in the consideration of the use of these antiseptic dyes.

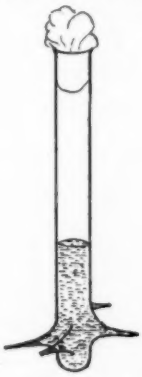


FIG. 2.—"Artificial Wound."

Use of Antiseptics in Wounds

(1) *Is it justifiable for the surgical pessimist who distrusts his own cleanliness to use antiseptics in an attempt to cover up his own deficiencies?*

The only reasonable answer to that is that the surgeon should so improve his methods that he would cease to be a pessimist. All the antiseptics in common use are toxic in some degree to the human organism as well as to bacteria, and are to be avoided wherever possible.

(2) *Is it possible, by the use of an antiseptic, to destroy an infection in a freshly inflicted wound before the bacteria have had time to grow out?*

In the last war at a base hospital in France I examined series of wounds which had been specially treated with carbolic acid, and compared them with others which had not been so treated. So far as the bacterial content went the carbolic-treated wounds were worse than the others.

Later in the war, a series of observations was made in which wounds were surgically cleansed, treated with various chemicals, and then primary suture was performed. It was found that the results were essentially the same whether the usual chemical antiseptics were used or not. They did no good, and apparently little harm.

I made some *in vitro* experiments which bear on the question whether it is easy to *sterilize* a contaminated wound with a chemical antiseptic. I made an "artificial wound" by drawing out a few processes from a glass test tube, so that the tube imitated the cavity of a war wound, except that the processes were less complicated and, of course, the walls could not be invaded by the bacteria (*see* fig. 2).

Serum containing a variety of bacteria from septic wounds was incubated in the tube, and after twenty-four hours it was dressed by inverting it to allow the serum

to run out, and then filling it with the antiseptic. On the first day the antiseptic was allowed to act for twenty minutes, and then it was emptied out, fresh serum replaced, and the tube was incubated for twenty-four hours. The flora was unaltered. On the next day one hour's application of the antiseptic was allowed, but there was no sign of sterilization of the tube. Later the antiseptic was allowed to act for twenty-four hours, but on emptying out the fluid and replacing it with serum there was still a copious growth. This result was obtained with all the antiseptics tested, viz. phenol, eusol, Dakin's solution, brilliant green, and acriflavine.

An experiment of this kind makes it seem unlikely that it would be possible to *sterilize* an infected wound by means of a chemical antiseptic (other than a clean cut, which in war is a rarity). I might here quote from an article which I wrote in the *Journal of Surgery* in 1919 :—

" During last summer I examined the packs removed from 75 cases of fractured femur on arrival of the patients at the base. These packs were mostly soaked in flavine, but there were also a certain number of B.I.P.P. or plain gauze pads. In all cases I found microbes present, and there seemed to be little difference between the bacterial content of the different varieties of pack."

(3) *Is it possible, by the use of antiseptics, to combat the infection in a septic wound in which the bacteria have grown out and invaded the tissues which have, in their turn, reacted to the infection ?*

Such a wound is full of pus, and the walls are infected well below the surface. Pus cells are polynuclear leucocytes, and they have a considerable antibacterial power. This can be shown in a very simple experiment. A drop of pus from a septic wound is placed on an agar plate, and a coverslip is gently placed on it. After incubation no growth of bacteria is seen in the pus, but there may be a few colonies around where, by the weight of the coverslip, infected fluid has been extruded beyond the limit of the cells.

If, however, the pus cells are killed by any method which will not kill the bacteria, an entirely different picture is seen. Multitudes of colonies appear throughout the pus. Simple methods of killing the pus cells without damaging the bacteria are : (1) Heating to 50° C. (2) Freezing and thawing. (3) Applications of a poisonous chemical such as carbolic acid.

The immediate effect of applying a chemical antiseptic to a wound can be easily ascertained by making impression preparations of a septic wound before and after such an application. Such observations were made on relatively clean granulating wounds, and it was found that immediately after washing the wound with an antiseptic there is a more copious growth of bacteria in these impression cultures. This is doubtless due to the pus cells being killed or washed away by the chemical, leaving many bacteria which are free to grow out.

The fact that in a septic wound the pus cells are powerful antibacterial agents makes it important to study the relative potency of the commonly used antiseptics on leucocytes and on bacteria. This can easily be done by using fresh blood as the culture medium, and I have published (Fleming, 1924) the results obtained with the common antiseptics when tested in this manner.

When the chemical was used in a weak concentration there was no action on leucocytes or bacteria, so that the resultant growth was exactly as the control. As the strength of the chemical was increased the leucocytes were interfered with, so that there was an increased growth of bacteria, until a concentration was reached in which every microbe grew out. It was only with stronger concentrations that the bacteria were inhibited.

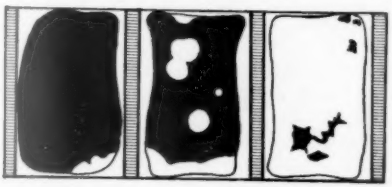
We have, then, with these chemicals, three phases as the concentration increases : (1) Indifferent. (2) Antileucocytic. (3) Antibacterial (only when the leucocytes are destroyed).

Carbolic acid is, if used strong enough, an antiseptic, but if it is added to blood in a concentration of about 1 : 700 it renders that blood a first-class culture medium and might, in certain circumstances, be used with advantage in blood culture.

One exception to the usual result is seen in connexion with the antiseptic dyes. These act slowly on both bacteria and leucocytes, and when the simple experiment alluded to above is made the leucocytes have time to destroy the bacteria before they are themselves destroyed by the chemical. When acriflavine was introduced (Browning *et al.*, 1917) it was shown that it inhibited the growth of bacteria in concentrations of 1 : 20,000 or less, but that when phagocytic experiments were made it required about 1 : 500 of acriflavine to seriously reduce the phagocytic power of the leucocytes. Thus it appeared that acriflavine was much more active on bacteria than on leucocytes.

These results have been widely copied. In these experiments, however, the dye was allowed to act on the leucocytes only for a few minutes.

I have shown (Fleming, 1917) that when acriflavine is allowed to act on leucocytes for a period of a few hours, a concentration of the chemical far lower than that which interferes with bacterial growth will seriously interfere with leucocytic function. This has recently been questioned, so I made a fresh series of experiments, this time testing the effect of acriflavine on the bactericidal power of human blood. Various concentrations of acriflavine were mixed with equal volumes of defibrinated blood, and then after four and a half hours, 50 c.mm. of these mixtures were infected with 2·5 c.mm. of a suitable dilution of a hæmolytic streptococcal culture and incubated in slide cells.



Control No acriflavine | Acriflavine 1 : 810,000 | Acriflavine 1 : 270,000

FIG. 3.—Blood mixed with acriflavine for 4½ hours, then infected with hæmolytic streptococci and incubated in slide cells. Clear areas represent hæmolysis due to growth of streptococci.

The result is shown in fig. 3, from which it is clear that a dilution of 1 : 810,000 damaged leucocytic function to some extent, and that a dilution of 1 : 270,000 acting on blood for four and a half hours rendered it a much better culture medium for a hæmolytic streptococcus.

In my opinion the best simple test for the possible efficacy of an antiseptic for use in a septic wound is that I have described, where the chemical is mixed with defibrinated or deleucocyted blood, suitably infected, and then the mixtures are incubated whenever possible in slide cells.

Human blood is a good fluid to use in the test, as it is very constant in its composition, and any antiseptic used in a wound has to act in a fluid more or less akin to it. Deleucocyted blood has no antibacterial action on the common microbes which infect wounds, so the test in deleucocyted blood gives a simple measure of the bacteriostatic power of the chemical. When defibrinated blood containing its full complement of leucocytes is used, then the action of the chemical on the leucocytes is also manifest.

If in this test it can be shown that the chemical is more strongly antileucocytic than it is antibacterial, it is extremely unlikely that such a chemical will be effective as a direct antiseptic in a septic wound.

It seems clear that, as in a septic wound there is a natural antibacterial element provided by the normal tissue reaction, the ideal antiseptic should be one which would not harm the leucocytes in concentrations which would inhibit the bacteria, so that the pus cells and the antiseptic could exercise a synergic action. This is what

happens with the sulphonamide compounds which are used for their general antibacterial action, but there are reasons why they should be ineffective when introduced to a *septic* wound as local antiseptics. I would like, however, to draw your attention to the action of mercurial salts in human blood on the hæmolytic streptococcus. (This is a specific reaction which, so far as I know, only occurs with this organism.)

If dilutions of mercuric chloride are mixed with defibrinated human blood suitably infected with hæmolytic streptococci, and incubated in slide cells, there is a zone of concentration (from about 1 : 40,000 to 1 : 160,000) when no growth occurs although there is growth in a 1 : 20,000 concentration. In deleucocyted blood there is copious growth throughout. This experiment has been figured in the *Proceedings*, 1931, **24**, 808.

The result in the deleucocyted blood shows that the chemical by itself cannot inhibit the growth of the streptococci. The control cell with the defibrinated blood shows that the blood itself cannot inhibit, but yet there is complete inhibition by the combination of defibrinated blood and certain weak concentrations of the mercury salt, although when this chemical is used in a concentration of 1 : 20,000, which interferes with the leucocytes, there is no inhibition.

This action of mercury salts resembles the action of the sulphonamides in that it is only evident when a small infection is present, and that it is especially manifest on the hæmolytic streptococcus.

Physiological Action of So-called Antiseptics

I would like to draw attention to the fact that some of the more popular antiseptics —the hypochlorites—have a physiological action quite independent of their direct antiseptic action. Carrel's treatment of a septic wound was probably the most popular in the last war, and I have shown that by this method the chemical remained in antiseptic strength in the wound for not more than ten minutes. However, Dakin's fluid, or chloramine T, induces a greatly increased transudation of fluid from the walls of the wound, and so drains the infected walls of the wound. This is brought out in fig. 4 which shows the rate of transudation from the walls of an infected wound before, during, and after the application of the chemical.

The drainage of the infected walls of a wound seems at least as important as drainage of the wound cavity, but while it is a basic surgical teaching to drain the cavity, little attention seems to have been paid to the drainage of the infected walls.

It seems likely that the benefits obtained by the intermittent instillation of Dakin's fluid into a wound depend more on this physiological effect than on any direct antiseptic action.

Practical Application of Antiseptics.

There does not appear to be a good case for the local use of chemical antiseptics in a really septic wound in which the bacteria have grown out and invaded the walls. In such wounds chemicals such as the hypochlorites might, with advantage, be used for their physiological action in draining the infected walls quite irrespective of their antiseptic action, which has been shown to be transitory.

The experience of the past and the experimental evidence indicate that it is not possible to sterilize serious war wounds by the local application of an antiseptic. It may be, however, that in times of stress, surgical treatment of the recently inflicted wound would have to be postponed, and in such a case the *thorough* application of an antiseptic would, in many cases, delay the growth of the bacteria. If this result could be achieved it would be worth while, even if the chemical did injure some of the tissue cells.

Acriflavine or another member of the same series would be a suitable chemical to employ in these circumstances, as it has a powerful bacteriostatic action on a small infection, and as its deleterious action on cells is slow. The surgeon should, however, never forget that these local applications of chemicals are only a second best, and that at the earliest possible moment the wound should be surgically cleansed and the antiseptic treatment discontinued.

I have already (1940) given reasons why the sulphonamide drugs are unlikely to act as local antiseptics in septic wounds in which the bacteria have grown out, and which are filled with pus. The presence of very large numbers of bacteria or of peptones completely inhibits the action of these compounds. In the freshly inflicted wound, however, bacteria are present only in small numbers, and there is no pus, so it is possible that the local application of the sulphonamide drugs would induce sufficient bacteriostasis to tide over the interval until the wound could be dealt with surgically.

In the sulphonamide drugs the choice lies between sulphanilamide and M & B 693.[1] Sulphanilamide is soluble to the extent of 1 : 100, and M & B 693 1 : 1,000. Sulphanilamide has a bacteriostatic action on a small inoculum of hæmolytic streptococci in a concentration of 1 : 500,000, and M & B 693 in 1 : 4,000,000. There is, therefore,

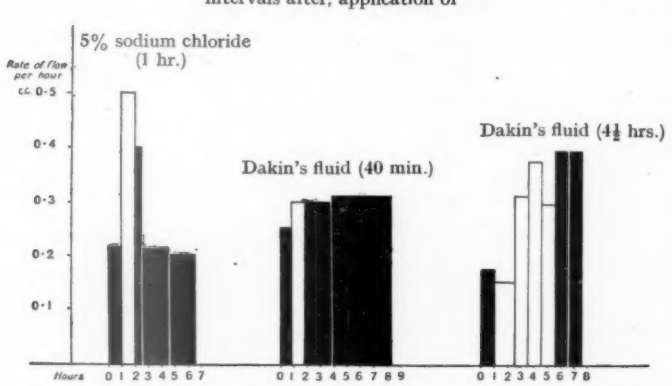

Rate per hour of transudation of lymph into a wound before, during, and at intervals after, application of
5% sodium chloride (1 hr.)
Rate of flow per hour
cc. 0·5
0·4
0·3
0·2
0·1
Dakin's fluid (40 min.)
Dakin's fluid (4½ hrs.)
Hours
0 1 2 3 4 5 6 7
0 1 2 3 4 5 6 7 8 9
0 1 2 3 4 5 6 7 8

FIG. 4.—Black columns = Before and after. White columns = During application.

little difference in the solubility-bacteriostatic ratio between the two chemicals. As regards their interference with leucocytic function, sulphanilamide has, in blood, an antileucocytic action in a concentration of 1 : 800, whereas semisaturated M & B 693 (1 : 2,000) in blood has no antileucocytic action. Thus the bacteriostatic-antileucocytic ratio is in favour of M & B 693, and if the chemical is applied as a powder or paste it seems probable, for this reason, that M & B 693 is the more suitable. It must not be forgotten, however, that the sulphonamide drugs only have an effective action on some of the bacteria which invade war wounds, and that if sufficient time elapses some of the insensitive ones will grow out till they are present in very large numbers, and will induce the emigration of masses of leucocytes. The action of the chemicals will then be completely inhibited, and their continued application will be useless, except for their general effect after absorption from the wound.

Summary

In the study of antiseptics attention should be given to the bacteriostatic action rather than the bactericidal action.

[1] Since this paper was written I have had the opportunity of making some tests with Sulphathiazole—another of the sulphonamide group of chemicals. This substance is *in vitro* at least as potent as M & B 693 on streptococci, and it is much more active on staphylococci, *B. coli*, *B. pyocyaneus*, *B. influenzæ* and some other organisms which may infect wounds. Reports have been published showing that it also functions as an efficient bacteriostatic agent *in vivo*. Because of its potency and its wide range of activity it would seem that sulphathiazole should be the most effective of the sulphonamide drugs for application to an infected wound with the object of inhibiting the infection until the wound can be surgically cleansed.

By a suitable arrangement of the conditions of an experiment, naturally occurring antibacterial agencies can be made to appear much more powerful than the usual chemical antiseptics.

Dakin's fluid in a wound loses its antiseptic power in less than ten minutes, so that in the Carrel-Dakin method of treatment there was no antiseptic in the wound for one hour and fifty minutes out of every two hours.

The affinity of the antiseptic dyes for dressings is illustrated.

Experiments are cited :—

(1) Indicating that it is unlikely that it is possible to sterilize a war wound with a chemical antiseptic. (2) Illustrating the antibacterial power of pus. (3) Illustrating the antileucocytic power of chemical antiseptics. (4) Showing the synergic action of mercury salts and leucocytes on the hæmolytic streptococcus.

Attention is drawn to the physiological action of hypochlorites in draining the infected walls of a wound.

It is suggested : (1) That antiseptics are not indicated in a septic wound where the bacteria have grown out and invaded the walls. (2) That while efficient surgery is the most effective method of dealing with a contaminated war wound, there might be occasions where surgery would have to be delayed, and then an antiseptic might be useful as a bacteriostatic. The antiseptics whose properties are most suited for such a purpose are members of the acridine series, and the sulphonamides.

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Dr. Dorothy S. Russell and Mr. Murray A. Falconer[1] : One of the principal criticisms levelled at the use of antiseptics in wounds is the allegation that they are more damaging to the tissues than to the bacteria. This allegation is unfortunately true for most surgical antiseptics. It explains why in the treatment of recently inflicted traumatic wounds most surgeons have rightly come to rely, for the control of infection, more on the thorough cleansing of the wound together with the excision of all contaminated and devitalized tissues than on the use of antiseptics. In traumatic wounds of the brain, however, it is often impossible to perform as complete a débridement as in wounds of other parts of the body, and therefore in cerebral wounds the use of antiseptics for the control of infection is more necessary than in other wounds. In this connexion it is vitally important that the antiseptics which we apply to the brain should not damage it. Comparatively little attention, however, has hitherto been paid to the reactions produced in human tissues by various surgical antiseptics.

At the instigation of Professor Hugh Cairns we have investigated various surgical antiseptics in order to find out which is the least harmful to cerebral tissues. We selected those antiseptics which possess widely acknowledged germicidal properties and which appear to retain these properties when applied to wounds. The method which we adopted was to operate on anæsthetized rabbits with full aseptic precautions and to expose the left cerebral hemisphere. After making a few minute scratches in the arachnoid membrane we applied the antiseptic to the surface of the brain by placing a piece of lintine thoroughly soaked in the antiseptic in contact with it for ten minutes. We also injected a little of the antiseptic into either the left or right

[1] Abstract of paper which will be published in full elsewhere.

hemisphere and then sutured the wound. The animals were killed at intervals ranging from one to eight days later and the brains examined macroscopically and microscopically.

Control Experiments

This method of course inflicted a slight but unavoidable amount of trauma upon the brain. Before we could evaluate the various antiseptics we had to ascertain what were the effects of our operative procedures. We did this by arranging a series of control experiments in which, instead of antiseptics, we used isotonic saline buffered to pH 7·4. Most antiseptics in clinical use are definitely acid or alkaline ; we found that the range of pH in those we tested was from 2 to 12. Moreover, in many hospitals and clinics it is customary to use ordinary water for making up or diluting antiseptics. We therefore controlled our observations by investigating the effects produced by isotonic saline buffered to pH 2·2 or pH 10 and by distilled water.

With neutral saline we observed only minimal degrees of reaction in the brain. Microscopically the leptomeninges showed slight focal hæmorrhage and proportionate inflammatory reaction where they had been exposed at operation, and the site at which saline had been injected was represented by a streak of hæmorrhage surrounded by active microglial cells. A few of the superficial neurones were shrunken and hyperchromatic, but for the most part the cortex presented normal appearances. The results obtained with neutral saline thus afforded a good standard for comparison in the experiments with other solutions. With salines at pH 2·2 and pH 10 we obtained slightly more reaction in the form of slight necrosis and severer leptomeningeal hæmorrhage associated with patchy degeneration and necrosis of the superficial neurones. When distilled water was substituted for saline we observed more extensive necrosis of the cortex. From these experiments it was clear that whereas the brain will withstand fairly acid or alkaline solutions for short periods of time, it is more seriously damaged by grossly hypotonic solutions. The logical deduction from our observations with various salines and distilled water is that all solutions which are to be applied to the brain should be rendered isotonic and as nearly neutral as possible.

Experiments with Antiseptics

We tested a wide range of surgical antiseptics, employing them in the concentrations which are recommended for application to wounds in general (*see* table). In the preparation of our solution we tried to apply as far as possible the principles of isotonicity and neutrality. We found no difficulty in rendering our solutions isotonic, but it was often impossible to achieve neutrality because precipitation of the active principle occurred. We then had to be content with buffering our solutions to a point as near neutrality as was compatible with maintaining a stable solution.

TABLE OF ANTISEPTICS INVESTIGATED.

I. *Acridine series*—			
Acriflavine in distilled water	.. ..	0·1%	pH 2
Acriflavine in saline	.. .. ..	0·1%	pH 2
Acriflavine in saline..	.. .. ..	0·1%	pH 7·2
Euflavine in saline ..	.. .. ..	0·1%	pH 7·2
Euflavine in saline ..	.. .. ..	0·05%	pH 7·4
Proflavine in saline..	.. .. ..	0·1%	pH 6·2
2 : 7-diaminoacridine in saline	.. ..	0·1%	pH 6·2
II. *Coal-tar series*—			
Dettol in distilled water	.. .. ..	5%	pH 12
Dettol in saline	.. ..	5%	pH 7·4
" Modified " dettol in saline	.. ..	5%	pH 8·4
" Modified " dettol in saline	.. ..	5%	pH 8·1
Supersan in saline	.. ..	5%	pH 8·2
III. *Halogen series*—			
Azochloramid in saline	.. .. ..	0·03%	pH 7·4
Azochloramid in triacetin	.. .. ..	0·2%	pH 4
Eusol	.. ..		pH 9

IV. *Organical mercurial series*—			
Metaphen in saline	0·1%	pH 10
Metaphen in saline	0·05%	pH 10
Merthiolate in saline	0·1%	pH 10
Merthiolate in saline	0·05%	pH 10
Phenyl mercuric nitrate in saline.. ..	0·08%	pH 10
Phenyl mercuric nitrate in saline.. ..	0·04%	pH 10
V. *Oxidizing agents*—		
Hydrogen peroxide in distilled water ..	3%	pH 4
Hydrogen peroxide in saline	3%	pH 7·4
VI. *Sulphonamide series*—		
Soluseptasine in saline	3·3%	pH 10
Soluseptasine in saline	3·3%	pH 7·4

With a few important exceptions the antiseptics which we investigated caused serious hæmorrhage and necrosis in the brain. The two principal exceptions were proflavine sulphate and 2 : 7-diaminoacridine hydrochloride, both of which, when applied in a concentration of 0·1% in isotonic saline buffered to pH 6·2, proved hardly more harmful than neutral isotonic saline. On the other hand acriflavine and euflavine, two other members of the acridine group, consistently caused intense hæmorrhage and necrosis wherever they came into contact with the brain. We are unable to account for the striking contrast in the effects of such closely related substances. It is probable that differences in chemical constitution are responsible. Moreover, proflavine and 2 : 7-diaminoacridine are pure compounds, whereas acriflavine and euflavine are mixtures of acridine compounds, and may vary in composition from sample to sample. In our view it is unfortunate that the generic term " flavine " has been applied collectively to these antiseptics because it has tended to obscure the differences that exist between individual members of the group.

None of the remaining antiseptics which we tested gave such favourable results as proflavine and 2 : 7-diaminoacridine. The coal-tar derivatives, dettol and supersan, both emulsions of a chlor-xylenol, when applied in buffered isotonic solutions, produced effects which, while not quite as mild as those seen with proflavine and 2 : 7-diaminoacridine, were yet a great improvement on acriflavine and euflavine. The halogen group was unsatisfactory. Azochloramid, an organic chlorine compound held by many to be superior to dichloramine-T, produced very variable results, some batches of solution being mild in action while others caused intense hæmorrhage and necrosis. Despite repeated attempts we were unable to account for or control this variability. Its solution in triacetin caused intense necrosis, as did eusol. The organic mercurial compounds all produced considerable hæmorrhage and necrosis in 0·1% concentrations, although merthiolate (0·04%) was fairly mild in its action. Hydrogen peroxide, which has no appreciable antiseptic action in wounds, but which is widely used in neurosurgery as a cleansing and hæmostatic agent, produced superficial fragmentation of the tissues accompanied by necrosis and hæmorrhage. Soluseptasine, which we selected as a representative of the sulphonamide drugs on account of its high solubility, was mild in its action.

Conclusions

Our experiments indicated that proflavine sulphate and 2 : 7-diaminoacridine hydrochloride are greatly superior to all the other antiseptics that we tested in that the damage which they cause to the brain is minimal. Both of these substances have been shown to be potent bactericidal agents in the concentrations in which we employed them. The latter compound is of recent introduction, but proflavine has been acknowledged for over twenty years. Proflavine as well as acriflavine has been proved to retain its efficiency when applied to wounds. Many investigators, including Neufeld, Schiemann, and Browning, have shown that in a high percentage of experiments in mice and guinea-pigs they are capable of sterilizing wounds which have been inoculated an hour or so previously with cultures of virulent organisms

such as *Streptococcus*, *Pneumococcus*, and *Bacillus diphtheriæ*. We therefore feel that in recommending proflavine sulphate (0·1% in isotonic saline buffered to pH 6·2) for application to wounds of the brain we are supporting an antiseptic which is both potent against bacteria and yet innocuous to the tissues.

Professor L. P. Garrod : Antiseptics can help in cleansing a wound, will deodorize it, prevent the access of further infection, and prevent the transference of infection to other cases, but that they can make all the difference between a wound being septic or not is discredited. This sceptical attitude dates from the Great War, when antiseptics were said to have been well tried and to have failed. There are special reasons for this alleged failure which have been overlooked. In the first place, the average gunshot wound is a most unpromising field for antiseptic treatment ; when it consists of a long track with a foreign body and dirt at the end of it, the deeper part of it cannot be treated at all by an application which, to be effective, must reach the whole of its internal surface. The possibilities of antiseptic treatment can be fairly judged only in reasonably open wounds capable of thorough irrigation. I beg you not to be depressed by the results of Professor Fleming's experiment with a test tube drawn out by blow-pipe into a number of thin lateral spikes. These narrowly tapering branches which prove incapable of disinfection have no equivalent in the body unless in wounds involving bone. They are rigid, whereas the crevices in soft tissues bordering a wound are elastic and mobile. It should not be beyond the wit of the surgeon to devise a means of ensuring that such crevices are penetrated by an antiseptic solution ; its injection under pressure through a fine jet would probably secure this effect. A second and even more serious reason for the failure of antiseptic treatment in the Great War was the inevitable delay in applying it. The period which elapses between the infliction of a wound and the invasion of surrounding tissues by bacteria is two hours or more. An antiseptic applied during this period has only to destroy bacteria in the cavity of the wound ; applied later it has to attack them in the tissues, a vastly more difficult task involving new factors, notably that of tissue penetration. The difference between prophylactic treatment, which is possible only for a few hours, and treatment applied when infection is already developing or even frankly in progress, is therefore immense, and it is astonishing that this distinction is so disregarded. This time factor must always operate against the success of antiseptic treatment in military surgery, where casualties can often not be brought in for several or many hours. The primitive antiseptic methods used in France in the early part of the Great War were in any case not calculated to succeed. If it be granted that for reasons such as these antiseptics did not in fact get a fair trial at that time, the present attitude to them is to that extent unjustified, and a more open mind in inquiring what they can do and how best they can be used is called for. A defeatist attitude is indeed a strange and unnecessary confession of failure at a time when the much more difficult problem of internal antisepsis has been largely overcome. Now that it is possible to destroy bacteria even in the circulation, it is surely not impossible to attack them when they are merely lying in a wound cavity and therefore directly accessible.

What I have further to say concerns the methods by which the suitability of an antiseptic for wound treatment can be judged. Of three principal methods, clinical trial is the most obvious, but in my submission should come last, both because it needs to be directed by information obtained in other ways, and because it is not a method which can easily yield significant results. Accidental wounds are too various in their site and extent and in the nature of their bacterial contamination to afford a proper test of prophylactic action, unless such a test be conducted on a very large scale. The conditions of test can be better regulated in the experimental animal, since wounds of determined extent can be identically contaminated in as many animals as may seem necessary and then treated by different methods. Experiments such as these by several workers in three different countries have agreed in showing that fatal infection by virulent streptococci can be averted by treatment of the wounds with acridine compounds at any time within the first two hours after their

infliction and contamination with these bacteria. Phenol, mercury perchloride, and other commonly used antiseptics consistently fail in such experiments. This is solid evidence that prophylaxis is feasible, and cuts across a multitude of objections that conditions in the body, as distinct from the test tube, militate against antiseptic effect. The third possible method of study is the purely *in vitro* experiment, which can be designed to assess the effect of an antiseptic on bacteria either under quite simple conditions or under conditions more or less resembling those existing in the body. The almost infinite variety of technique employed for this purpose makes even the approximate correlation of different workers' results exceedingly difficult. It is deplorable that no generally recognized *in vitro* method exists for testing the suitability of antiseptics for application to wounds. A simple and appropriate method would be to determine the degree of disinfection in a mixture containing 50% of blood at 37° C. in a fixed time of, say, two hours.

It is also necessary to know something of the action of an antiseptic on body cells. I think the importance of this factor can be exaggerated ; if a wound can really be disinfected by something which also damages leucocytes, this is a small price to pay for such an effect ; leucocytes are easily and quickly replaced, and unless there is demonstrable damage to fixed tissues as well, this degree of " toxicity " is no bar to usefulness in wounds involving connective tissue and muscle. There is the same lack of a generally accepted and appropriate method of test here. Parenteral methods of administration are a test of the action of the antiseptic on sensitive and vital structures with which in ordinary use it does not come into contact at all. Two *in vitro* proceedings are available—application to tissue cultures, and admixture with fresh blood followed by observation of the effect on leucocytes, this being judged either by motility or by phagocytic capacity. Acridine compounds come well out of such tests, and 1 : 2,000 acriflavine, although it reduces leucocytic activity does not abolish it ; this observation is in apparent conflict with that of Professor Fleming, who found that as little as 1 : 274,000 acriflavine interfered with leucocytic activity in the slide cell. The variability in composition of acriflavine underlies some of the inconsistencies in results obtained with it, but this discrepancy is so extreme that it raises the question whether some peculiarity in the conditions existing in the slide cell may account for it. Certainly the most appropriate method of testing toxicity for a particular tissue is *in vivo* application to that tissue and histological study of the results. The facts so elicited by Dr. Dorothy Russell and Mr. Murray Falconer about the effect of antiseptics on the brain are of the highest practical value, and should lead anyone requiring an antiseptic of the highest degree of harmlessness to select proflavine.

Summary

(1) Prevention of infection and treatment of infection already in progress are to be sharply distinguished in considering the place of antiseptics in wound treatment.

(2) Prevention is feasible in open wounds treated within a few hours.

(3) Available evidence points to the acridine compounds as the most suitable agents for this purpose.

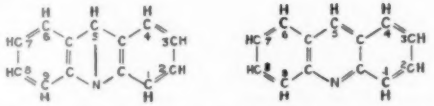
Dr. Malcolm C. Manifold (Department of Biochemistry, Oxford University) : *The Effect of Certain Antiseptics on the Metabolism of Brain Tissues in vitro.*[1]— This preliminary investigation was carried out at the suggestion of Professor R. A. Peters, in order to determine whether brain tissue was damaged from the point of view of normal metabolism when various antiseptics were severally added to the medium in which the brain tissues were respiring.

The respiration experiments were carried out in Dixon-Barcroft manometers at a temperature of 38·2° C. and a pH of 7·3 using air or oxygen according to the conditions required. The brain tissue was used either in the form of slices, minced tissue, or a finely ground dispersion, and in the experiments where slices or minced tissue were used, the medium was a Ringer-phosphate solution of pH 7·3, which gives

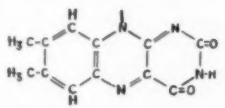
[1] Abstract of a paper which will shortly be published elsewhere.

the same values for the respiratory quotient of brain as a bicarbonate-Ringer solution. In certain experiments the medium contained, in addition, substrates such as glucose or sodium pyruvate. The dispersion medium was a buffered isotonic solution of potassium chloride with the addition of sodium fumarate, which is an essential intermediary in the pyruvate oxidation system of the brain and must be added to systems made in the form of tissue dispersions. To this medium, glucose or sodium pyruvate was added in certain cases.

The main results of this investigation are those appertaining to the use of some derivatives of acridine. These compounds are frequently but erroneously known as flavines, for example acriflavine, proflavine, &c. It is, in passing, very important to realize the fact that acridines do not belong to the true " flavin " series, of which riboflavin, a member of the vitamin B_2 complex, is an example. In order to demonstrate the great difference between the two series of compounds, the following structural formulæ are presented.



The above are alternative formulæ for acridine.



The above formula shows the ring system for riboflavin.

It will be seen that these two sets of formulæ are very different, and the importance of realizing this difference is strongly emphasized. In this, and all other communications on this subject from this Department, the numbering of the acridine ring will be as shown in the above diagrams. This is pointed out because there are alternative ways of numbering such ring systems and it is very important to realize which system is being used in the discussion of any particular problem, as failure to do so would lead to a deal of confusion.

The brain tissue used in these experiments was obtained from either human, rabbit, or pigeon sources, but the results do not differ fundamentally from one source to another.

In the case of the acridine antiseptics, the concentration used was in general 1 : 1,000, and the final pH of the mixture was adjusted to 7·3.

The first experiments deal with the effect of acriflavine on the ability of brain tissue to utilize oxygen. In all the experiments quoted, duplicate determinations were made and were adequately controlled.

Acriflavine as normally prepared is a mixture of the hydrochlorides of 2 : 8-diaminoacridine and 2 : 8-diaminomethyl acridonium chloride, and may thus vary considerably in composition. Hence the results obtained on the physiological effects of such a mixture are of no great value since they cannot be traced to the effect of any one pure compound. The results with acriflavine (1 : 1,000) showed clearly that it was very toxic to brain tissue and caused a 70% inhibition of the respiration of brain slices placed in a medium with or without glucose. This figure of 70% was the average result of six experiments.

Neutral acriflavine or euflavine showed a slightly lower toxicity (though probably not significantly so), than acriflavine, as far as brain slices were concerned, for the average percentage inhibition of the respiration in seven experiments was 62, and the same inhibition occurred using minced brain and euflavine. Three experiments in which euflavine was tested on brain dispersions showed a further increase in

respiratory inhibition to 79%, which increase one might reasonably expect, for in dispersions the rapidity with which a substance can attack the enzyme systems responsible for respiration is greatly increased.

The use of proflavine sulphate (which is 2 : 8-diamino-acridine-sulphate) in a series of six experiments on brain slices, resulted only in an average figure of 36% for the percentage inhibition of the respiration. In a further four experiments on minced tissue this figure increased to 54%, while three experiments on dispersions showed a percentage inhibition of 73. It is thus clear that as far as brain slices are concerned proflavine sulphate is far less toxic than either acriflavine or euflavine. Since the technique involving the use of tissue slices more closely parallels the conditions under which antiseptics are used clinically than that in which minced tissue or dispersions are used, we shall for true comparative purposes stress the results for slice experiments.

The next experiments were carried out using 2 : 7-diamino-acridine-hydrochloride, which proved to be a remarkable compound in that three experiments on slices showed the low figure of 28% for the inhibition of respiration, while three experiments on minced tissue and three on dispersions showed respectively only 34 and 31% inhibitions.

While proflavine sulphate has been known for a number of years, 2 : 7-diamino-acridine-hydrochloride is a relatively new compound synthesized by Linnell in 1936. A survey of the literature relative to the antiseptic values of the various acridine compounds reveals the fact that acriflavine has been extensively used as an antiseptic and has been reported not to cause any extensive damage to the tissues. Earlier results did not, however, include any references to the use of acriflavine on brain tissue. Therefore the results of Mr. M. A. Falconer and Dr. Dorothy Russell, coupled with those reported in this paper, seriously question the advisability of employing acriflavine as an antiseptic for general use, especially since proflavine sulphate is as efficient a bacteriostat as is acriflavine.

Neither acriflavine nor proflavine sulphate are superior in bacteriostatic power to 2 : 7-diaminoacridine-hydrochloride, and while the experiments of Mr. Falconer and Dr. Russell with this compound were not as extensive as those on proflavine sulphate, they did show that the 2 : 7 compound had no deleterious effect on the brain tissues.

It would thus appear that on the evidence from bacteriological, biochemical, and histological sources, proflavine sulphate is definitely more suitable than either acriflavine or euflavine in the treatment of wounds.

The bacteriostatic values of 2 : 7-diaminoacridine have been well demonstrated, and the biochemical evidence, although by no means complete, would suggest that this compound may turn out to be the most suitable of all these derivatives for general use. Further biochemical and histological evidence with regard to this substance is awaited with interest.

Certain other antiseptics were tried out by means of these respiration techniques. Azochloramid, used in the recommended concentration of 1 : 3,300, was found to be very toxic to brain slices, the percentage inhibition of the respiration being of the order of 80. The action of this substance was tested at various concentrations and it was found that at concentrations of 1 : 45,000 the azochloramid no longer interfered with respiration. Many experiments were carried out using this compound, and its behaviour was found to be irregular in that one could not be sure that two experiments carried out in an exactly similar manner would give reproducible results. A full discussion of these results will shortly be published.

Two mercurial antiseptics, merthiolate and metaphen, have been examined, and the results with these were unsatisfactory. Metaphen seemed to be unstable, for in each case where this compound was used, the medium at the end of the experiment was found to be very alkaline, an observation which had not been noted with any of the other antiseptics.

Experiments on soluseptasine, a sulphanilamide derivative, showed that this compound caused a quite high inhibition of the respiration of brain slices. In no

way were the results with these latter three compounds comparable with those obtained with either proflavine sulphate or 2 : 7-diaminoacridine-hydrochloride.

The utilization of oxygen by the tissues is a sensitive process, and is liable to be affected by adverse changes in the cell environment. Probably all such changes would be clinically harmful. The phenomenon of inhibition of respiration by these antiseptics, as set forth in this report, certainly has significance in view of the fact that it may be correlated with pathological changes as instanced by the histological work on this subject.

It would, however, be a mistake to assume that the *in vitro* results can be directly related to changes taking place *in vivo*.

So far, I have not found any reliable method of deciding whether the inhibitory action of these antiseptics is reversible or not. In the absence of evidence on this point it must not be assumed that there is necessarily permanent damage to the tissue concerned. Nevertheless, it is possible that those cells which have been intimately in contact with the antiseptic do not recover their normal metabolic function. In any case the conditions obtaining *in vivo* may not be compared with those of our experiments where thin slices of tissue are surrounded on all sides by the medium and antiseptic, and partially at any rate penetrated by the antiseptic. These tissue slices are not as it were " backed up " by a great mass of actively living tissue as would be the case in a wound. Hence the *in vivo* effects for a given strength of antiseptic might be expected to be less severe.

In conclusion, although the results do not afford a precise index of the extent of the injury which may occur clinically from the use of an antiseptic, they can nevertheless be used to indicate the relative toxicities of various substances to a vital and sensitive mechanism, and in this respect they have been well supported by bacteriological and histological evidence.

I wish to express my appreciation of the kind help and criticism afforded me by Professor R. A. Peters, and to thank the Rockefeller Foundation for a grant in aid of this work.

Colonel E. M. Cowell (*in absentia* read by Dr. Downie): *Morbid anatomy of gunshot wounds.*—This subject is discussed in the various textbooks on War Surgery and with special reference to air-raid wounds in Mitchiner and Cowell's " Medical Organization and Surgical Practice in Air Raids ".

The factors to consider are :—

(1) Infections, aerobic and anaerobic, which will be present in wounds received in fighting in most of the countries of Europe.

(2) Massive destruction of tissue with comminution of bone in wounds caused by even minute fragments of air bombs.

Principles of treatment.—In the last war, principles of treatment were evolved, and by 1918 were giving good results. Treatment at first consisted in removal of the foreign body and establishment of drainage, together with the following sequence of method :—

(1) Application of pure carbolic.
(2) Iodine.
(3) Salt packs and hypertonic saline lavage.
(4) B.I.P.P. and the coloured antiseptics.
(5) Carrel-Dakin continuous irrigation.
(6) Excision and primary suture.
(7) Excision, vaseline, or soap packs and secondary suture.
(8) Winnet Orr's method of excision and débridement and immobilization in plaster of Paris.

From this list of methods it will be seen that in the early stages surgeons were beaten by the profound sepsis of all wounds ; they failed to rely on careful surgery with the removal of infected tissues and foreign bodies, but attempted to kill bacteria by the use of strong germicides. These methods failed, although the Carrel-Dakin

treatment was an advance. When more surgical teams were available, and organization was better, a greater proportion of wounds dealt with at the casualty clearing station, excision was perfected, and the results enormously improved.

In the Spanish war local antiseptics were hardly used at all. Trueta and other surgeons whose work I saw in Barcelona relied on débridement and immobilization in plaster of Paris.

Constitutional methods.—The use of sera, vaccines, and intravenous therapy may have a subsidiary place in the treatment of war wounds, but in my opinion the best results will be obtained by good organization, rapid evacuation to surgical centres where careful surgery is carried out by trained traumatologists. The operation consists in wide excision of all damaged tissues, removal of foreign bodies, and immobilization in plaster of Paris.

The treatment of wound shock and hæmorrhage by blood transfusion is important.

Evacuation of casualties.—The subject of " The Effect of Antiseptics on Wounds " in war can only be properly discussed when front-line conditions are taken into consideration.

Front-line treatment of gunshot wounds.—The layout of the modern battle-field is very different from that familiar to some present in the last war. The wounded soldier will have a shell dressing or first field dressing applied as early as possible and then probably have to lie under cover till a lull in the fighting occurs or till darkness falls before he can be carried in to the regimental aid post (R.A.P.).

These dressings are only very mildly antiseptic and iodine is no longer used in the Army Medical Services. Under favourable conditions he will soon be got away by field ambulance bearers—say an hour's hand-carry—some distance by wheeled stretcher, and then by ambulance car to the advanced dressing station (A.D.S.) a a few miles back from the R.A.P.

His stay here should be brief if there are enough vehicles and the roads are not being shelled too badly. His dressings are not interfered with unless there is severe unchecked hæmorrhage. Cases are marked in order of urgency and sent on to the main dressing station (M.D.S.) some 7–10 miles further back—a slow journey in the dark, over congested roads with shell fire, shell holes, possibly gas, and a tired driver who does not know the way very well. Very little surgery will be attempted at the M.D.S. and no disinfection of wounds is possible. Casualties will be sent back by cars of the motor ambulance convoy (M.A.C.) as rapidly as possible. This stage of the journey will occupy one to two hours, probably more at night, and ends with admission to the surgical centres casualty clearing station.

The total distance covered from the most forward areas to the C.C.S. may be from 25–30 miles, and the time lag from six to twenty-four hours.

At the C.C.S.—Expert surgeons will be available—six or eight teams, each with two or three tables, will be required to deal with large numbers of casualties. After débridement, irrigation with some mild antiseptic may do no harm, but in my opinion it is safer to rely on conscientious surgery and if lavage soothes the surgeon's conscience, saline does less harm than anything else.

Summary

(1) Strong antiseptics cannot remove germs or dead tissue.

(2) Careful ablation of dead and damaged tissues, together with removal of foreign bodies is the essential principle, followed by immobilization.

(3) Increasing the patient's resistance by blood transfusion and administration of fluids is more useful than relying on chemical measures or the use of strong antiseptics.

Section of Medicine

President—Sir MAURICE CASSIDY, K.C.V.O., M.D.

[*April* 23, 1940]

Some Observations on a Pressor Principle in the Urine of Hyperpietics

By E. IDRIS JONES, M.D.

ATTEMPTS to demonstrate the presence of a pressor substance in the blood or urine of hypertensive subjects have given very conflicting results. In the blood, any pressor principle which may be present is usually very rapidly adsorbed or inactivated and whole blood or extracts usually give negative results. In the case of urinary extracts, the picture is complicated by the presence in the urine of some normal subjects of a substance or substances which give a pressor effect when injected into animals. Also, this pressor effect, although given by the urine of some hypertensives, is absent in the urine of others and the type curve obtained does not correspond with the curve given by known pressor substances such as adrenaline or pituitrin. There is some evidence too that pressor substances develop in stale urine during the process of fermentation, and this may well account for some of the discordant results obtained. The general conclusion is that no definite substance has been constantly demonstrated in the urine, which can be incriminated as the factor causing essential hypertension. It is probable, however, that not all cases of essential hypertension have a common ætiology and consideration of the possibility of some cases being due to posterior pituitary overactivity is justified. It seems established that most, if not all, endocrine glands may either overact or underact in certain pathological states. The syndrome of paroxysmal hypertension due to pheochromocytoma of the suprarenal medulla is already well defined, and on theoretical grounds there is no reason why the posterior lobe of the pituitary may not also overact and cause certain cases of hypertension.

In a hypothetical case of overactivity of the posterior pituitary we should expect to find hypertension, disordered carbohydrate metabolism, increased excretion of chlorides in the urine, a diminished excretion of urine (or at least an abnormal response to forced drinking) and possibly achlorhydria and anæmia. These last two we should expect to be present only if the amount of pituitrin secreted was very large. Also as pituitrin is excreted in the urine but appears to be adsorbed in the blood we should expect to find it in the urine in appreciable quantity, but its demonstration in the blood would be difficult.

Here is an account of a patient who satisfied most of the foregoing criteria. An athletic male, aged 26, was suffering from anæmia of a hyperchromic type, which responded readily to administration of liver extract, but relapsed at once on discontinuing liver. As can be seen from Table I, after the blood-count had been restored to approximately normal the second time, the discontinuance of liver therapy did not cause a relapse. During a routine examination of the patient it was found that his blood-pressure was 190/110 in both arms and slightly higher in the legs, thus excluding coarctation of the aorta. His urine was normal in all respects and renal

TABLE I.—SUMMARY OF BLOOD-COUNTS.

Date	Hæmoglobin (%)	Erythrocytes (per c.mm.)	Colour index	Leucocytes (per c.mm.)
March 7 (liver given)	78	3,400,000	1·26	2,800
March 15	86	4,080,000	1·16	9,100
March 23	84	4,770,000	1·04	6,300
March 30 (liver discont.) ..	92	5,430,000	0·93	3,500
April 5 (liver given)	88	3,320,000	1·45	3,850
April 15 (liver discont.)	102	4,650,000	1·18	5,250
May 11	92	5,480,000	0·92	7,700
May 30	100	4,840,000	1·14	4,900
July 25	80	5,500,000	0·80	4,900
August 7	100	5,040,000	1·08	—
September 22	100	5,030,000	1·08	6,650

function tests performed later were normal. Owing to the coincidence of a hyperchromic anæmia and arterial hypertension in a young man with no demonstrable renal disease a common cause for both was sought. Dodds and his co-workers had recently published their work on experimental anæmia production in rabbits following the administration of pituitrin, so the possibility of this patient having a posterior pituitary overactivity was considered. A blood-sugar curve was therefore done. This was found to be grossly abnormal (Table II). Examination of the stomach

TABLE II.—BLOOD-SUGAR CURVE OF THE PATIENT IN MAY 1937.

Fasting level	Number of minutes after 50 g. of glucose were given			
	30	60	90	105
129 mgm. ..	338	286	314	270

BLOOD-SUGAR CURVE OF THE PATIENT IN SEPTEMBER 1937.

Fasting level	Number of minutes after 50 g. of glucose were given			
	30	60	90	120
146 mgm. ..	238	177	228	204

contents showed achlorhydria both before and after histamine. There was little in the patient's history to suggest any marked antidiuretic factor being present, and at no time had he fainted or passed into a coma, as has been known to happen in normal men and cases of diabetes insipidus receiving pituitrin. Because of his anæmia, hypertension, abnormal carbohydrate utilization and achlorhydria, his blood and urine were examined for the presence or absence of detectable quantities of pituitrin. Extracts were made of his blood and urine, using the method adopted for pituitrin from pituitaries. The blood extract was negative on two occasions tested. On injection of the urinary extract into a spinal cat, a marked pressor response was

obtained, the curve being identical with that obtained by giving pituitrin. By comparison with standard doses of pituitrin it appeared that his urine contained about 1 unit of pituitrin per 200 c.c. of urine. Of more significance was the antidiuretic assay. The extract caused complete inhibition of diuresis in rats, the response being again equivalent to about 1 unit of pituitrin per 200 c.c. Commercial pituitrin also contains a factor which causes dispersal of melanosomes—so-called "melanophore dilatation"—in animals. This factor is probably manufactured by the anterior pituitary in man and the pars intermedia in animals, but utilizes the path of discharge of the posterior pituitary. Injection of an extract of the patient's urine into frogs caused marked melanosome dispersal, whereas normal urine extract produced no change in control frogs. The extract also showed other characteristics of pituitrin, namely destruction of activity by alkali and retention of activity following acidification or boiling. The extract therefore showed many of the characteristics of pituitrin and corresponded in action with no other known substance.

Repeated extracts were made of the patient's urine at intervals over a period of six months, and the previous results were confirmed each time except when the urine had become strongly alkaline and the substance had therefore probably been destroyed. A striking fact emerged during these repeated experiments. The amount of pituitrin-like substance in the urine gradually diminished, and in September, i.e. after six months' observation, only a very small quantity was detectable. This decrease corresponded with a fall in the patient's blood-pressure and in September his blood-pressure had returned to normal (Table III). This seems to be the strongest

TABLE III.—BLOOD-PRESSURE READINGS.

April 8	190/110	July 1	164/110
April 23	205/110	July 13	165/100
May 13	165/108	August 16	160/104
June 1	162/105	September 23	130/80

evidence that this pituitrin-like substance bore a causal relationship to the hypertension. The blood-sugar curve of the patient was also much nearer normal in September than when he was first seen. Since that time until September 1939, i.e. two years, the patient has been normal, but since the outbreak of war I have lost touch with him. There is one point which merits further discussion. The patient was excreting an antidiuretic substance in the urine yet he was secreting urine normally. It appeared as if he had developed a resistance to this factor. In order to test this he was injected with 5 units of commercial pituitrin. This should inhibit diuresis in a normal man, yet the patient at the end of one and a half hours passed a quantity of normal urine. He obviously had acquired a resistance to the antidiuretic factor. A similar resistance has been noted in animals. This last experiment indicates as conclusively as it was possible in this case that it was the posterior pituitary which was responsible for his condition, the gland overacting, but after a period of months returning to its normal condition.

Since this case eight other patients with hypertension have been examined. The urine only was extracted and in five of these no trace could be found of a pressor substance resembling pituitrin although pressor bodies were present in two. These gave responses in a spinal cat similar to those observed by other workers, namely an initial fall in pressure then a transient rise. There was no melanosome-dispersing principle present. In the other three of the eight cases, a melanosome-dispersing principle was present and a pressor effect similar to pituitrin was given. These cases were unfortunately not investigated fully for the antidiuretic factor, and but one had

an abnormality of carbohydrate metabolism. They were suggestive, however, of posterior pituitary overactivity, but that is as much as we can say at present.

In the search for further cases exhibiting this syndrome particular attention must be paid to the association of hypertension with disordered carbohydrate metabolism. A hyperchromic anæmia and achlorhydria may be also associated, but these are not essential features of the syndrome and may be absent except in severe cases. Before a case can be accepted the urine should be shown to contain a substance which has pressor and antidiuretic effects, a melanosome-dispersing effect on frogs, and the substance should resist boiling and be destroyed by alkalies.

Section of Neurology

President—GEOFFREY JEFFERSON, M.S.

[*March* 21, 1940]

Stenosis of the Aqueduct of Sylvius

By JOE PENNYBACKER, F.R.C.S.

(*From the Nuffield Department of Surgery, Oxford.*)

FOR nearly a century it has been known that hydrocephalus is occasionally associated with occlusion of the aqueduct of Sylvius. But it is only since we have had a more complete knowledge of the circulation of the cerebrospinal fluid that the strategic importance of the aqueduct has been appreciated. Here is a small tube, in the adult human brain some 20 mm. long by 2–3 mm. in diameter, which is asked to convey all the cerebrospinal fluid secreted in the lateral and 3rd ventricles down to the outlets in the 4th ventricle. A minute lesion which in other parts of the brain might cause no trouble at all may narrow the aqueduct so that the flow of the cerebrospinal fluid is obstructed, and hydrocephalus results.

In general, such lesions may be either neoplastic or non-neoplastic. The first group includes tumours of the quadrigeminal plate and other parts of the mid-brain which may compress the aqueduct and produce interesting neurological abnormalities; but, as they are generally infiltrating tumours in an inaccessible situation, treatment at best affords only temporary relief of symptoms, and if we could be sure of the diagnosis, it may be asked whether this treatment should ever be surgical. Nevertheless, this group deserves consideration in the differential diagnosis from the more benign lesions which may produce a very similar clinical state, but which have considerably better prospects of cure.

In the non-neoplastic group, the commonest pathological process seems to have been described first by Spiller in 1902. A boy of 19 who had suffered from periodic headache since childhood was admitted to hospital with symptoms of increased intracranial pressure and signs which pointed to the diagnosis of cerebellar tumour. He died suddenly, and examination of the brain showed that the aqueduct was almost completely obliterated, but to the naked eye the structure of the mid-brain otherwise appeared normal and no evidence of tumour was seen. Histological examination showed that the stenosis had been effected by a proliferation of the normal subependymal glia around the aqueduct. In 1936, Stookey and Scarff collected from the literature 16 cases of non-neoplastic stenosis; in the 12 of these in which an adequate histological examination was made, this proliferation of subependymal glia appeared to be the underlying pathology. These subependymal glial cells (and especially their fibrillar elements) seem to proliferate, and may cause a true stricture of the aqueduct from without; or the proliferation may break through the ependyma to form tufts within the lumen which may be valve-like or membranous; or there may be a more or less regular spread of the glial processes within the aqueduct, encroaching on its lumen from within. In yet another variety, the aqueduct may be split up into a number of tiny channels which may be almost invisible to the naked

eye ; the aqueduct becomes a swamp through which the cerebrospinal fluid seeps, but with considerable difficulty.

This paper concerns 18 cases of non-neoplastic stenosis of the aqueduct which have been observed in Professor Cairns' Clinic. This diagnosis cannot be established until the mid-brain is examined histologically after death, and unfortunately six of the cases in this series have been so confirmed. But these six cases, and a study of other recorded verified cases, have given sufficient information about the clinical state and the ventriculographic appearances to warrant the diagnosis in the unconfirmed cases.

Juvenile Type

The clinical picture is not uniform, but the following case is fairly characteristic :—

G. O'S, aged 10, was admitted to the Radcliffe Infirmary on August 25, 1939, referred by Mr. John Kelly. He was born at full time, and apart from having a big appetite and being very plump, was, according to his parents, a perfectly normal child until three years before admission, when he became clumsy with his hands, and very apt to spill things at the table. His hands were shaky, and about eight months before admission this tremor of the hands became so marked that he was treated in hospital for two months as a case of chorea. He did not improve, however, and one month before admission he began to suffer from severe headache and occasional bouts of vomiting. It was these symptoms which led to his admission to the Radcliffe Infirmary.

On examination he was a fat child, 4 ft. 10 in. tall, weighing 7 st. 2 lb. He had a large head, 57 cm. circumference, with a cracked-pot note on percussion, and a blowing systolic murmur was audible all over the skull. He was cheerful and co-operative, but had occasional bouts of headache which seemed to distress him considerably. There was no dysarthria. He had bilateral papilloedema, 3 D, but the visual acuity was normal and there was no defect in the visual fields. The pupils and external ocular movements were perfectly normal, and the functions subserved by the other cranial nerves were likewise normal. In the limbs there was no definite dystonia or weakness, but there was a vibratory tremor of the outstretched limbs, rather coarser than that seen in hyperthyroidism, and exaggerated on purposive movements. He was a little unsteady on his feet, but was able to walk without support. There was no sensory disturbance. X-rays of the skull showed general enlargement, convolutional thinning, and separation of the sutures ; erosion of the sella was so marked as to raise the question of the lesion being in the immediate neighbourhood of the sella. The cerebrospinal fluid was normal.

The diagnosis rested between stricture of the aqueduct, suprasellar tumour, and a high vermis tumour. A ventriculogram showed gross internal hydrocephalus, a dilated 3rd ventricle, and the shadow of the aqueduct ending just beyond the 3rd ventricle. This was additional evidence for the diagnosis of stenosis of the aqueduct. At operation, a fistula was made between the 3rd ventricle and the subarachnoid space by splitting the lamina terminalis.

The post-operative convalescence was interesting in that the child developed a peculiar mutism for two to three days ; his physiological state was perfectly satisfactory, and he was alert enough to co-operate in quite a complete neurological examination. But he would not talk—until on the morning of the third day he suddenly started talking quite normally. This mutism has been observed in two other cases in which this operation has been done.

He was discharged from hospital three weeks after operation. The bone-flap was flush with the skull, the papilloedema had subsided, and the spinal fluid pressure was 70 mm. cerebrospinal fluid. The hydrocephalus thus appeared to have been relieved by the operation. He was free from headache, but the tremor of the hands and the unsteadiness of gait persisted.

He was readmitted to hospital five weeks later because the headache had recurred, and he had become very drowsy and incontinent of urine. On examination, two months after operation, the decompression was bulging, and he was clearly suffering from progressive hydrocephalus. The signs were much as on the previous admission, but in addition there were slight weakness, moderate ataxy, and dysdiadokokinesis down the left side of the body. It was suggested that these left-sided signs were due to a subdural collection of cerebrospinal fluid over the right hemisphere, but a further ventriculogram showed only severe hydrocephalus and no subdural collection. As we felt that we might be missing a cerebellar tumour, a posterior fossa exploration was made, but the

cerebellum appeared to be perfectly normal. The child derived no benefit from this additional decompression, and a week later the fistula in the 3rd ventricle was re-explored. It was found to be still patent but the hole was smaller than when it had been first made. It was enlarged to a diameter of about 1 cm. The effect of this operation on the intracranial pressure was apparently satisfactory as the bone-flap was sunken in, and the ventricular and spinal fluid pressures remained low. But the child died three weeks after this last operation from a staphylococcal infection which was probably acquired at the second operation (cerebellar decompression).

At autopsy the hole in the lamina terminalis was widely patent, and although the right Sylvian cistern was obliterated by operative adhesions, the left one and the cisterna basalis were ballooned out, suggesting that the fistula was effective. To the naked eye, the aqueduct appeared to be almost completely obliterated. Histologically this obliteration was shown to be due to proliferation of the subependymal glia.

This case illustrates what may be termed the juvenile type of the affection in which the hydrocephalus develops while the skull is still soft enough to stretch before the expanding ventricles. They are plump children with large heads. Although it is usually the recent onset of headaches and visual failure which brings them for treatment, the long duration of the lesion is betrayed by the large head and by the history of tremor of the hands, clumsiness or a little unsteadiness of gait, sometimes for years before the onset of pressure symptoms. With the papillœdema there may be secondary optic atrophy with corresponding affection of visual acuity. In one case it was difficult to say whether the atrophy was of the primary or secondary type, and there were bilateral central scotomata, presumably due to compression of the optic nerves by the dilated 3rd ventricle. Of oculomotor signs there may be limitation of upward movement of the eyeballs, squint, nystagmus, and sluggish reactions or immobility of the pupils, but three of the six verified cases have shown no abnormalities of the pupils or external ocular movements. Other cranial nerve palsies are not common. In the limbs a very common and characteristic feature is the fine vibratory tremor, especially of the hands, which was described in the case above; and this may be the first or only abnormality of motor function. Hypotonicity and diminution of tendon reflexes may occur, or there may be spasticity, exaggerated tendon reflexes, and extensor plantar responses. The motor signs are usually bilateral, although they may be more marked on one side. Sensory abnormalities are rare. Incontinence of urine is common and may occur early in the course of the affection, before any signs or symptoms of increased intracranial pressure. Genital development is commonly delayed. One of these cases was associated with von Recklinghausen's neurofibromatosis and one with syringomyelia.

The cerebrospinal fluid pressure is raised, but the fluid itself is normal. X-rays of the skull show the general enlargement and convolutional thinning, separation of the sutures and possibly some erosion of the sella. Thirteen of our cases were of this juvenile type.

Adult Type

There is another interesting group of five cases in which symptoms first appeared between the ages of 18 and 25. These patients all came for treatment because of symptoms of increased intracranial pressure. They all had papillœdema, and one of them had no other abnormal signs. In the others the most striking feature was a disturbance of the pupils and external ocular movements; defective upward movement of the eyeballs, skew asymmetry on conjugate deviation, and pupils which were virtually fixed to flashlight, but reacted well to accommodation-convergence. The neurological examination otherwise was negative, but in two cases there was tremor of the hands as in the juvenile group. One of these patients also had Recklinghausen's neurofibromatosis. Ventriculograms showed dilated lateral and 3rd ventricles, with defective filling of the aqueduct, and this appearance, together with the oculomotor signs, led to the diagnosis of tumour of the pineal gland or vicinity. They were all operated on (and had subsequent deep X-ray therapy); and they are all alive and

well now, after periods of seven, six, four and a half, and three years. These results suggest that the lesion was not neoplastic and is more likely to have been a benign stenosis of the aqueduct.

The diagnosis still rests on accurate ventriculograms. This clinical picture of increased intracranial pressure with signs of hydrocephalus may suggest a suprasellar tumour, a pineal or mid-brain tumour, or a tumour in the posterior fossa, especially in the upper part of the vermis. The ventriculogram shows dilated lateral and 3rd ventricles and perhaps a funnel-shaped termination of the aqueduct shadow just distal to the 3rd ventricle, and this may be sufficient to exclude suprasellar and pineal tumours. But the same appearances may be seen in some cases of tumours of the cerebellum and mid-brain, and in the present state of radiographic technique it may be impossible to say more than that the obstruction is below the 3rd ventricle. With improvements in technique, however, we may expect to get the right answer in a greater proportion of cases. Lysholm and Twining have described the characteristic deformities of the 3rd ventricle and aqueduct seen in lesions which may be confused with non-neoplastic stenosis of the aqueduct.

Treatment.—Attempts have been made to dilate the narrowed aqueduct by the passage of a small catheter from the 4th ventricle up into the 3rd ventricle. This was a blind procedure, capable of doing a great deal of damage to important structures in the neighbourhood of the aqueduct, and in 1922 Dandy discarded it with the comment that it could not be permanently effective. But he described a new operation for the relief of the condition: he had punctured the "floor of the 3rd ventricle" (evidently the lamina terminalis) in six cases of stenosis of the aqueduct, to allow the cerebrospinal fluid to escape from the 3rd ventricle into the supratentorial subarachnoid space without having to traverse the narrowed aqueduct. He thought this might be effective in all forms of obstructive hydrocephalus in which the obstruction was distal to the 3rd ventricle, although he made no claims for the success of the method. I have not been able to discover his more mature views about the value of the procedure, nor what happened to the six cases.

In the following year, Mixter passed an operating ventriculoscope through the lateral ventricle into the 3rd ventricle via the foramen of Monro, and punctured the floor of the 3rd ventricle under direct vision. This case was apparently successful, but again the method was not exploited.

In 1936, Stookey and Scarff reported six cases of stenosis of the aqueduct in which they had punctured not only the lamina terminalis but also the floor of the 3rd ventricle, thus allowing a double exit into the capacious cisterna interpeduncularis (basalis) as well as into the cisterna chiasmatis. This procedure was successful in three out of four non-neoplastic cases, and in one case of mid-brain tumour there had been a comfortable survival for seven months until the date of their report.

Other procedures which have been tried are (1) opening of the 3rd ventricle by splitting the corpus callosum; (2) temporal decompression; (3) cerebellar decompression.

In this present series, the results of these various procedures can be seen from the following tables:—

TABLE I.—JUVENILE TYPE (13 CASES).

I.—*Six cases proved by autopsy.*

		Treatment	Result
1	F. B.	Cerebellar decompression	Death on table due to wax embolus in lung
2	G.O'S.	Anterior 3rd ventriculostomy (Dandy); cerebellar decompression; exploration of 3rd ventriculostomy	Death from staphylococcal infection 3 weeks after last operation
3	M. D.	Double 3rd ventriculostomy (Stookey-Scarff)	Death 24 hours after operation (hyperthermia)
4	N. J.	Pineal exploration; splitting of corpus callosum	Death 1 month after operation
5	B. H.	No treatment	Death from infection 3 days after ventriculogram
6	L. M.	No treatment	Death 3 years after onset of symptoms

II.—*Six cases in which diagnosis was made by ventriculography.*

1	P. W.	Splitting of posterior part of corpus callosum	Temporary relief of symptoms. Death 10 months later. No autopsy
2	F. E.	Anterior 3rd ventriculostomy	*Satisfactory 1 year after operation
3	E. J.	Anterior 3rd ventriculostomy	Satisfactory 4 months after operation
4	B. C.	Anterior 3rd ventriculostomy	Satisfactory 2 years after operation
5	F. M.	Cerebellar decompression (+ X-ray therapy)	Satisfactory 3 years after operation
6	R. D.	Cerebellar decompression	Satisfactory 4 years after operation.

III.—*One case diagnosed on clinical evidence : no ventriculogram.*

1	O. R.	Cerebellar decompression	Satisfactory 3 years after operation

* In the results classified as " satisfactory ", the symptoms of increased intracranial pressure were relieved (without bulging of the decompression), and there was improvement in the neurological signs.

TABLE II.—ADULT TYPE (5 CASES).

Five cases in which ventriculogram showed obstruction below 3rd ventricle. The first four had deep X-ray therapy after operation as they were suspected of having pineal tumours.

		Treatment	Result
1	D. S.	Pineal exploration	Alive and well 7 years after operation
2	R. V.	Temporal decompression	Alive and well 6 years after operation
3	T. F.	Cerebellar decompression ineffective ; pineal exploration and splitting of corpus callosum	Alive and well 4 years after operation
4	R. I.	Cerebellar decompression	Alive and well 3 years after operation
5	G. B.	Cerebellar decompression	Recurrence of symptoms 3 months after operation. (Under observation at present)

The four patients who are alive and well are quite free of symptoms. No. 1 is serving as an A.R.P. warden, No. 2 is practising as a police court solicitor, No. 3 is a telephone operator, and No. 4 is serving in one of the armed forces.

TABLE III.—RESULTS OF VARIOUS PROCEDURES EMPLOYED IN TREATMENT OF STENOSIS OF AQUEDUCT.

I.—*Decompression operations.*			
A.	Temporal decompression (+ deep X-ray therapy)	Effective	1 case
B.	Cerebellar decompression	Effective	4 cases (2 + deep X-ray)
		Ineffective	3 cases
		Operative death	1 case
II.—*3rd ventricle operations.*			
A.	Pineal exploration and splitting of corpus callosum	Effective	2 cases (2 + deep X-ray)
		Ineffective	2 cases
B.	Anterior 3rd ventriculostomy (Dandy)	Effective	4 cases (? 3)
		Ineffective	(? 1)
C.	Double 3rd ventriculostomy (Stookey-Scarff)	Death after 24 hours	1 case

It is impossible to say from these results just what is the proper treatment of stenosis of the aqueduct. On physiological grounds, 3rd ventriculostomy seems to be a sound procedure. Splitting the lamina terminalis is an operation fraught with no great risks, and certainly in some cases it seems to be effective. The Stookey-Scarff operation is more dangerous, as the puncture of the floor of the ventricle usually has to be done blindly ; my single experience of it was not a happy one. Operations on the posterior part of the corpus callosum are more difficult and dangerous, and are apt to leave a permanent hemianopia.

A case can certainly be made for the external decompressions. Five of the best results in this series must be attributed to this method despite the assertion of

Stookey and Scarff that such operations are theoretically unsound. Indeed it is not easy to explain how these operations are effective, but that they may be so there can be no doubt. A cerebellar decompression will also occasionally disclose a tumour which would have been missed by a supratentorial operation. It may be that we should start by doing a cerebellar decompression ; if that is not effective, then a 3rd ventriculostomy. I would first split the lamina terminalis, and if that were not effective, puncture the floor of the ventricle at a subsequent operation. As we are dealing with an essentially benign condition, conservative operations carrying no great risks are to be preferred to more radical measures.

My thanks are due to Professor Cairns for access to his records and clinical material, and for advice and assistance in the preparation of this report.

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Section of Ophthalmology

President—MALCOLM HEPBURN, F.R.C.S.

[*March* 29, 1940]

Tarsectomy of all four Lids for Trachoma (*with slides*). — A. F. MACCALLAN, C.B.E., F.R.C.S.

This lady is a private patient who had suffered from trachoma for some years. When I saw her she had the second stage of trachoma with bleb-like excrescences of tarsal conjunctiva and of the conjunctiva of the fornix also in the left eye.

She was treated by " mechanical treatment " (expression and scraping) on two occasions as it was not possible to carry out combined excision of tarsus and conjunctiva of the upper lids while the conjunctiva was friable as the result of the numerous blebs.

Tarsectomy was performed on all four lids on March 15, just a fortnight ago.

The slides illustrate trachoma in different stages. One of them is from a case arising in Egypt and shows a very exaggerated papillary overgrowth. A section of trachomatous tissue reveals the marked lymphocytic infiltration. Another case shown is one in which the cicatrization is beginning and the epithelium is changing from the columnar type to a stratified type of scar tissue epithelium. The next example illustrates the fourth stage of trachoma, practically a cured stage ; it is a case in which all the active changes have ceased, and the hypertrophic fibrosis can be seen in the tarsus.

Bilateral Retrobulbar Neuritis.—C. DEE SHAPLAND, F.R.C.S.

T. G., male, aged 30.

History.—First attended Royal London Ophthalmic Hospital on 22.1.40, saying that for the previous three weeks he had been unable to see in the distance. There had been no pain.

On examination.—Vision in both eyes : Counting fingers at $\frac{1}{2}$ metre, improved with the addition of +0·50 D.sph. to $\frac{6}{6}$. The discs showed slight swelling on the nasal side with blurring of the margin. The fields were full and small paracentral scotomata were present. No other abnormal physical signs were found in the nervous system.

Wassermann reaction negative. Skiagrams of the skull showed no abnormality except some " fuzziness " of the outer table of the parietal bone.

He smokes 20–30 cigarettes a day. He has attended hospital regularly since his first visit and his condition remains the same.

This patient has been seen by many of my colleagues at the Royal London Ophthalmic Hospital and they have given various opinions as regards diagnosis. It has been suggested that the fundi are normal and that the condition is purely functional. I cannot agree with that, and I feel it to be a true retrobulbar neuritis. It has been suggested that he has a neuromyelitis optica, but there are no other physical signs or symptoms in the nervous system.

Discussion.—Miss E. E. CASS said that there was a round reddish area in each macula, which almost looked as if the patient had a commencing " hole " in this region.

Mr. E. F. KING asked whether the pupillary reactions were normal, and on Mr. Shapland replying that they were, Mr. King expressed the view that it was a functional case.

Dr. PERCIVAL HAY asked whether the onset was functional and if the condition in the one eye followed the other. He thought it must be a case of Leber's atrophy. He understood that the family history was not available. The man might be, however, an only child.

Mr. SHAPLAND replied that there was a three weeks' history and the visual failure was in both eyes together. With regard to Leber's atrophy he felt that was probably the right answer.

Melanosis of the Sclera.—E. F. KING, F.R.C.S.

P. W., male, aged 18.

First seen 5.3.40.

On examination.—Extensive right scleral melanosis. Right iris darker than the left. Cornea clear. Fundus normal. R.V. $\frac{6}{9}$.

Left eye: Nothing abnormal found. L.V. $\frac{6}{9}$.

Jaw-Winking.—P. G. DOYNE, F.R.C.S.

Pamela S., aged $2\frac{1}{2}$ years.

History.—It has been noticed that the lid of the left eye opens widely when the child eats, and this has been present since birth. She has teeth with no enamel and her mother and father have a similar condition.

On examination.—Both eyes are normal, but the left upper eyelid rises when she opens her mouth and falls when she closes it.

She has attended the Royal Dental Hospital and the Hospital for Sick Children, Great Ormond Street, and the dental condition has been diagnosed as a congenital hypoplasia of the enamel of the teeth. Eighteen members of the patient's family are affected in three generations.

? Heerfordt's Uveoparotitis.—ANTHONY PALIN, F.R.C.S.ED.

Mrs. D. O. M., aged 49.

History.—Treated by her own doctor for iritis in right eye in August 1939; apparent resolution slowly after two months. First seen by myself on 26.12.39 with acute iridocyclitis and optic neuritis in left eye following a severe cold.

Progress.—Within two days the iridocyclitis and optic neuritis developed bilaterally, with marked exudation in the left pupil. Resolution is occurring very slowly. Vision fell to $\frac{3}{60}$ in the worse (left) eye but both eyes have now recovered to about $\frac{6}{9}$.

Investigations.—No results of positive value. Wassermann reaction negative. Tuberculin skin test negative. Urine normal. Neurological and general examinations revealed no abnormality. General asthenia is marked.

Within the last month a small painless nodular enlargement has developed in the pre-auricular portion of the left parotid gland. No other glandular enlargements have been detected.

A survey of the patient's own doctor's medical records has revealed two findings of possible relevancy. In 1928 patient had an attack (her first) of mumps. In June 1939 (two months before the first known evidence of uveitis) an attack of pyrexia of undiscovered origin occurred and persisted for three weeks.

Blood-count (November 1939): R.B.C. 4,500,000; Hb. 80%; W.B.C. 5,000 with a slight relative lymphocytosis of 40%.

Outstanding features of this case are the absence of both polyneuritis and rash at any stage, and the occurrence of optic neuritis. Painlessness of the parotids compares with all cases reported except one, and pyrexia before the parotitis seems to be the rule. There is no sign or family history of tuberculosis. It is of interest that at the only four autopsies performed in this disease three showed miliary tuberculosis and the other pernicious anæmia.

In recent literature a comparison is being made between this condition and Boeck's sarcoidosis.

Discussion.—Mr. G. T. W. CASHELL said that he reported a case of this nature about six years ago. A section of the parotid gland showed typical giant cells, probably tuberculous in origin.

Mr. L. H. SAVIN said that the glands in these cases rarely if ever went on to caseation. Workers at the Johns Hopkins Hospital had recently carried out some fresh investigation which strongly supported the identification of uveoparotitis as a manifestation of Boeck's sarcoid. The skilled histologist could discriminate between tuberculosis and Boeck's sarcoid. Mr. Palin had used the term " polyneuritis " for the nervous symptoms, but the term was too narrow. In some cases there had been conditions which were obviously central nervous in origin rather than belonging to the peripheral nervous system only.

Mr. M. L. HINE referred members to an account of Boeck's sarcoid in the *British Journal of Ophthalmology* [1] with a discussion of its relationship to uveoparotitis. They had a similar case at Stanmore, who had started with a cyclitis in one eye last July, had had an attack of so-called " mumps " in October, and then developed cyclitis in the other eye. At Stanmore, Dr. Hickling found she had an enlarged spleen, but though this suggested the possibility of Boeck's sarcoid, no other characteristic signs were found by X-ray, and the tonsils were not visibly affected. No local treatment, combined with rest in bed, and fresh air for six weeks, did any good, but after she had two or three applications of deep X-ray therapy to the spleen and abdominal glands at Charing Cross Hospital, she at once began to improve, and now has reading vision in one eye. This may, of course, be merely a coincidence, as the prognosis in some cases of this affection is said to be quite good. When seen in mid-December the parotids of this patient were like those of Mr. Palin's patient, but by the beginning of February they were normal.

Mr. EUGENE WOLFF said he had seen a case which was diagnosed as Heerfordt's uveoparotitis in which the ophthalmic surgeon and all who looked after the case got swellings !

Mr. CASHELL said that he did try gold therapy in his case and the patient made a complete recovery. Injections of krysolgan were used.

For Diagnosis. ? Malignant Melanoma of the Choroid.—P. M. MOFFATT, F.R.C.S.

F. B., male, aged 47. Warehouseman.

6.11.39 : Complained that he had struck his head near the right eye against an iron bar.

On examination.—Small superficial wound below right eye, near orbital margin. R.V. $\frac{6}{9}$ c. — 1 D.sph. = $\frac{6}{6}$. L.V. = $\frac{4}{60}$.

Questioning disclosed that sight in left eye has failed in last two years, and especially in last six months. Latterly he has found that the left eye could see objects only on the left side.

Left fundus : A raised pigmented area above and involving the macula ; no detachment of the retina over it.

28.12.39 : The area seemed more raised and to be spreading. The fundus appearance and the visual acuity have remained unchanged.

The patient finds that he has to look a little to one side if he wants to see anything with his left eye, and therefore it is rather difficult to get an accurate scotoma chart of that area. At first I thought I had got two quite accurate records, but later the patient would not co-operate and I failed to plot the scotoma. The man refused to have the eye out. I would like to know if the condition is really malignant, and if so whether one should put pressure on the man to persuade him to have the eye out.

Discussion.—Mr. FRANK W. LAW said that it would be interesting while this case was under discussion to learn what was the general opinion as to the presence or absence of a scotoma with choroidal mole. The tendency was to say that with a choroidal mole there was no scotoma, whereas a scotoma was present when there was an established malignant condition, even if early. The question arose in this case. A good deal of importance did turn on the presence or absence of a scotoma in an ordinary choroidal mole.

[1] Osterblag, G., **23**, 145.

Mr. E. F. KING said that for some years he had watched a case of what he took to be an innocent melanoma of the choroid which had a small scotoma and had not increased in size. The appearance of the growth had not changed, nor was the scotoma altered.

The PRESIDENT said that he quite agreed with Mr. Law's opinion about the scotoma. It was a very useful method of deciding whether a melanoma was or was not increasing. In the present case the growth was so extensive and suspicious that he would not himself seek to retain the eye. The patient should be told that the condition was too dangerous to leave, even if there might be some doubt about its malignancy.

Traumatic Asphyxia with Optic Atrophy.—P. M. MOFFATT, F.R.C.S.

A. B., male, aged 37. Shopkeeper.

9.12.39: Was knocked down in the blackout, and subsequently it was noted that he was suffering from traumatic asphyxia. Three days after the accident, examination of the ocular fundi was made and he was found to have blurring of the left disc and pallor. He had noticed that he was unable to see properly with this eye. R.V. $\frac{6}{5}$, Hm. + 0·5. L.V. $\frac{3}{60}$, Hm. + 3·5.

On examination.—Extensive subconjunctival ecchymosis was found, but apart from the abnormality of disc already noted, the fundi were normal. No hæmorrhages were visible in the retinæ of either eye. The right field is normal and left field is much reduced on the temporal side especially.

Heuer (*Surg., Gynec. & Obst.*, 1923), in his review of 127 cases, reported in the literature, finds that 44 were examined ophthalmoscopically. 26 of these had no intra-ocular abnormality. In the remainder, hæmorrhages, œdema of the retina, and optic atrophy were noted. The optic atrophy, sometimes the sole finding, was found within a few days or after weeks or months.

The absence of hæmorrhages in many cases has been explained on the grounds that the intra-ocular pressure supports the blood-vessels. In this connexion it is interesting to note that the skin beneath the shirt band and other areas protected by the pressure of clothing frequently escape discoloration.

With regard to the optic atrophy, it is thought the cases coming on early are the result of hæmorrhages into the optic nerve or its sheath, whereas those in which the optic atrophy develops later are due to death of the ganglion cells caused by vascular stasis and œdema.

Film illustrating Gunn's Syndrome.—E. E. CASS, M.B.

Miss E. E. Cass exhibited a film illustrating Gunn's syndrome, sometimes described as " jaw winking ", which had been shown at the third Brazilian Congress of Ophthalmology at Bello Horizonte in July 1939, by Professor Pimental of Nictheroy (State of Rio de Janeiro), and which he had kindly lent her.

Professor Pimental had a case of Gunn's phenomenon occurring in a girl of 16. The case was congenital and unilateral; a few bilateral cases only had been described. In this case there was a partial right ptosis, and on pushing forward or opening the jaw the eyelid was raised. The term " jaw winking " is a bad one, as the characteristic feature is the raising, not the lowering, of the eyelid. It has been suggested that there was some connexion between the 5th and 3rd nerves in the post-longitudinal bundle to account for this condition. Professor Pimental wondered if this was some atavistic condition, and he noticed that when cats ate, as they opened their mouths they raised their eyebrows. This usually occurred only on the side on which the cat was eating.

The film which was shown included the movements of the girl patient, and also of certain cats while feeding.

[The report to be continued in the July issue, viz.:

Malignant Change in a Case of Melanosis of the Conjunctiva.—G. T. WILLOUGHBY CASHELL, M.B., B.S.Lond., F.R.C.S.Ed., and

Binocular Loupes.—F. A. WILLIAMSON-NOBLE, F.R.C.S.]

Section of Obstetrics and Gynæcology

President—W. GILLIAT, C.V.O., M.S.

[*March* 15, 1940]

Some Investigations on the Treatment of Sterility

By MARGARET MOORE WHITE, M.D., F.R.C.S., M.R.C.O.G.

(1) *Uterosalpingography and Insufflation*

Over a period of two years I have pursued investigations into the condition of the fallopian tubes in women complaining of sterility. Radiography following lipiodol injection into the uterus was employed for the earlier cases, but overcrowding of the X-ray Department limited the numbers that could be dealt with; the acquisition of a Rubin's insufflator a year ago enlarged the scope of my investigations. Since that time I have used the insufflator both in lieu of and in conjunction with lipiodol injection.

I have come to the conclusion that the employment of both means of diagnosis is essential in many cases, and that on the whole one can interpret more accurately the state of the fallopian tubes by a study of the kymograph tracing, and be able to give a more accurate prognosis regarding the likelihood of pregnancy, than one can from study of the radiograph alone.

On the other hand the therapeutic results from injection of lipiodol appear to be better than those from insufflation (*see* Table II); the heavy antiseptic oil (containing 40% iodine) seems to have a distinct therapeutic value. It may be that, on account of its antiseptic properties, foci of infection in the cervix are eradicated and abnormal mucous secretion lessened; possibly lipiodol has a stimulative action on ciliary movement in the fallopian tube or possibly by the excitation of peristaltic movements provoked by the presence of lipiodol, the rhythmic contractions of the tubes may, in their efforts to expel the oil, act advantageously on the ovum, especially after an injection timed just to precede ovulation.

Tubal insufflation and lipiodol injection were timed whenever possible, to take place in the week preceding ovulation, i.e. between the sixth and twelfth days of the menstrual cycle, so as not to interfere with a possible early implantation of the ovum; but in one instance in which insufflation was performed towards the end of the cycle, it was obvious later that implantation must have occurred previous to insufflation, which did not disturb the embedded ovum.

I believe that air embolism only occurs if trauma is inflicted or insufflation performed too near the onset of menstruation.

No significant difference as regards complications has been observed in the two methods.

Rubin's insufflator apparatus with kymograph attachment has been used to obtain the tracings which are the original ones recorded on the revolving drum. The pressure of CO_2 escaping from the cylinder is the same in each case, and the apparatus is adjusted so that CO_2 gas is not allowed to pass through the uterus into the tubes at a rate pressure flow greater than 30 secs. to produce a pressure rise of 100 mm. of mercury, hence each patient is similarly treated. The waves obtained denote peristaltic contractions of the tubes.

161 lipiodol injections have been given; unilateral salpingitis resulted in one patient in whom the radiograph showed the fallopian tubes to be obstructed, one other patient experienced pain in the pelvis with mild pyrexia for a few days but nothing abnormal was felt on vaginal examination, and as subsequent insufflation revealed patency of the tubes, these symptoms may only have been due to an iodine reaction.

141 insufflations have been given, repeated on some patients two and even three times; one patient has suffered from acute bilateral salpingitis following insufflation. A radiograph taken a week before showed that no lipiodol had entered either tube; I think that it was unwise to insufflate so soon after injecting lipiodol in such a case. Insufflation confirmed non-patency, revealed by the radiograph, denoting the existence of a diseased condition of both tubes.

In no case in this series has the radiograph shown that lipiodol had entered the pelvic veins following injection (Coventry, 1934; Kilroe and Hellman, 1933), nor was there any trace of lipiodol under the diaphragm in those patients X-rayed one year after treatment, though traces of lipiodol were present in the pelvis in one or two cases.

TABLE I.—LIPIODOL INJECTION INTO THE FALLOPIAN TUBES COMBINED WITH ENDOCRINE THERAPY.

	Aug. 1937 to June 1938	July 1938 to June 1939	July to Sept. 1939	Total Aug. 1937 to Sept. 1939
Number of cases	62	65	34	161
Husband's seminal analysis—				
Aspermia	13% } 21%	8% } 28·5%	4% } 29%	26·2%
Oligospermia	8% }	20·5% }	25% }	
Consented to examination	63%	75%	70%	69·3%
Non-patent fallopian tubes	17·7%	20%	23·5%	20·4%
Pregnant following lipiodol injection—				
Of the whole series	35·5%	26%	23·5%	28·3%
Of the possible series	47·8%	47·2%	47·0%	47·3%
Percentage of miscarriages	32	31	12·5	25·2
Pregnant again to term	9%	6%		7·5%
Average age of patient	30	30·8	31	30·6
Average number of years of sterility	5·7	5·7	5·9	5·8

TABLE II.—COMPARISON OF LIPIODOL INJECTION AND INSUFFLATION.

	Lipiodol		Insufflation	
Number of cases	161		48	
Husband's seminal analysis—				
Aspermia	8·3% }	26·1%	12·4% }	45·1%
Oligospermia	17·8% }		32·7% }	
Consented to examination	69·3%		68%	
Non-patent fallopian tubes	20·4%		23·0% } poor 15·0% }	38·0%
Pregnant—				
Of whole series	28·3%		10·4%	
Of those possible	47·3%		25·0%	
Average age of patients	30·6		30·8	
Average number of years of sterility	5·8		5·3	

Tables I and II show my results. The number of insufflations reported is small, but most of the 141 insufflations mentioned were given during the last four or five months, and follow-ups have been difficult. Although it is perhaps too early to assess results with confidence, the immediate effects have been to confirm the view that lipiodol injection is more successful than insufflation. Moreover, since the kymograph tracing enables us to recognize those tubes incapable of peristalsis, a fact which one is unable to ascertain from the radiograph, unless screening has been undertaken during the injection of the lipiodol, the aggregate of women incapable of pregnancy is, to our knowledge, higher and hence the percentage of successes in those in whom pregnancy is possible should be higher.

[Radiographs were shown illustrating different conditions of the uterus and fallopian tubes, including a bicornuate uterus, and bilateral hydrosalpinx.]

One can more readily ascertain the side of the tubal obstruction by lipiodol injections. During insufflation, on auscultation over the abdomen the escape of CO_2 from the tubes can be detected, but the side from which gas escapes cannot be ascertained with certainty and the coincident pain referred to one or other shoulder is not an indication of the side on which the tube is patent. The injection with lipiodol yields this information with precision.

[Kymograph tracings were shown illustrating the state of the fallopian tubes in different patients, some of which are reproduced here, viz., Charts I, II, III, IV.]

From the tracings it is apparent that one may diagnose the condition of the fallopian tube and hence be able to give a prognosis as to the likelihood of pregnancy, whereas the capability of peristalsis on the part of the tube is not indicated on a radiograph. Moreover, subsequent events have shown that when a tube is incapable of peristalsis it is not likely to propel the ovum to the uterus ; nor is pregnancy likely to supervene when the contractions are feeble and quickly decline in intensity, unless improvement follows treatment.

When lipiodol injection has demonstrated abnormality in the tubes, it is inadvisable to repeat the injection to confirm the findings or to ascertain the subsequent result of treatment, but insufflation may be carried out safely, and will often demonstrate the effect of the lipiodol injection.

(2) *The Effects of Follicular Hormone on Non-patent Fallopian Tubes*

Clauberg (1938) reported the results of the action of large doses of follicular hormone on the fallopian tubes. His first experiments were carried out on laboratory animals. He showed that if the infantile female animal was given repeated large injections of follicular hormone, a rapid development of the genital apparatus, including the fallopian tubes, resulted. Ten days after commencing injections with large quantities of Progynon B. Oleosum Forte there was considerable increase in the growth of the tube, widening of the lumen and hyperæmia.

Later Clauberg showed that a similar action could be produced if the hormone were given to women with an infantile uterus and fallopian tubes, and hence could be employed as a treatment in certain cases of sterility. He suggested that the tubal lumina could be so narrow that they would not fill with the opaque medium (lipiodol) injected into them, non-patency of the fallopian tubes being depicted on the X-ray plate, but that after a course of five injections each of 50,000 International Benzoate Units of Progynon B. Oleosum Forte at five-day intervals the lumina became patent and filled with the opaque material. He demonstrated the histological effects of the hormone on the tube by selecting two patients with " as similar endocrine function as possible " from whom it was intended to remove one or both tubes, and in the one case gave the above-mentioned large doses of hormone, using the second patient as a control. Similar sections were taken from the fallopian tubes removed

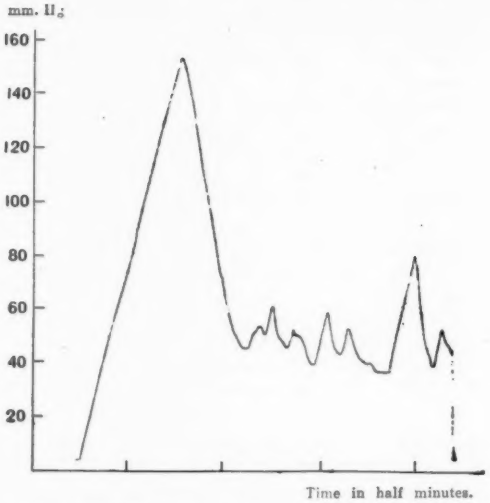

CHART I.—W. J. 12.7.39. Initial spasm, followed by good tubal contractions.

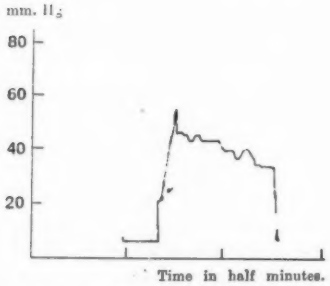

CHART III.—A. M. 27.6.39. Case of infantile uterus. Poor peristalsis.

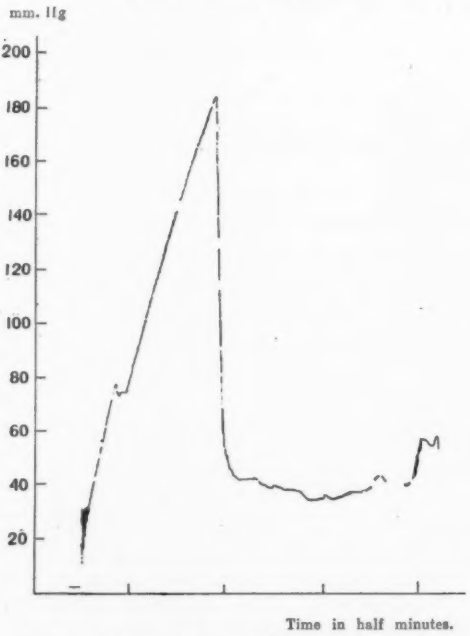

CHART II.—G. D. 29.10.39. Illustrating obstruction overcome; feeble peristalsis. Left shoulder pain.

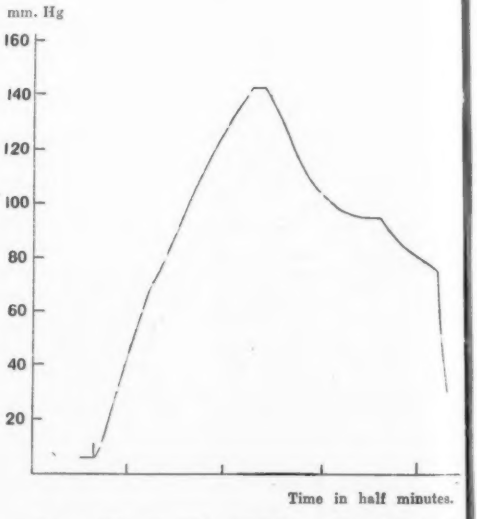

CHART IV.—M. O'D. 15.9.39. Rigid fallopian tubes incapable of peristalsis (history of general peritonitis).

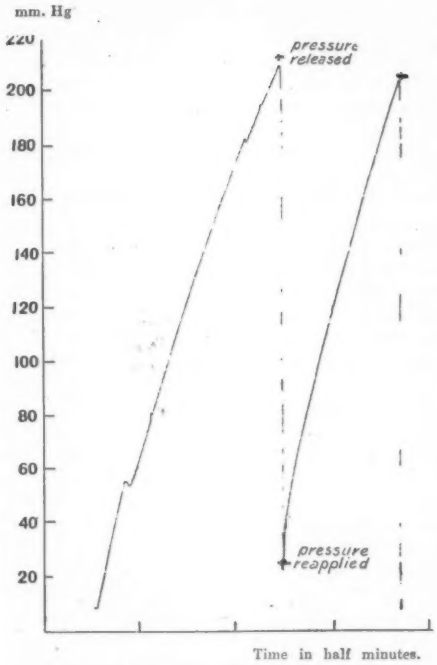

CHART V.—L. S. 19.7.39. Radiograph showed right tube obstructed at fimbrial end, the left in the ampullary portion. Right-sided pelvic pain felt during insufflation. (*See* Chart VI.)

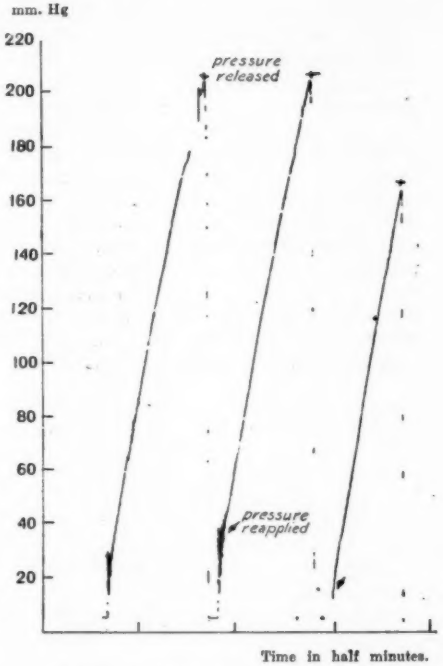

CHART VII.—G. M. 17.5.39. Radiograph showed tubes closed at fimbrial end; non-patent also on insufflation. (*See* Chart VIII.)

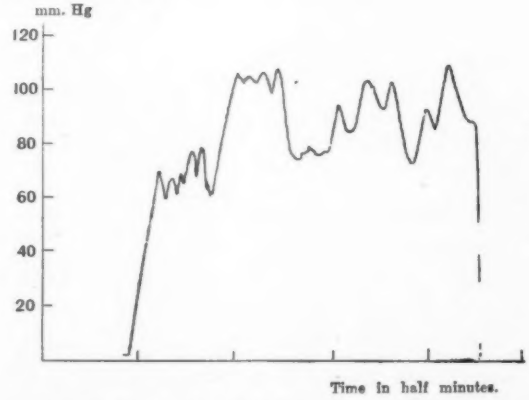

CHART VI.—L. S. 16.8.39. After injections. Air heard coming from both tubes. Right shoulder pain felt.

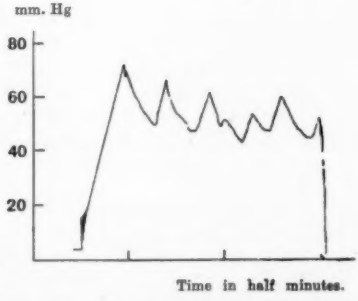

CHART VIII.—G. M. 21.6.39. After injections. Immediate shoulder pain felt. Tracing denotes patency at a pressure of 70 mm. Hg.

from the two patients operated on for some other pelvic disorder; the tube of the treated patient showing fresh proliferation most marked in the superficial epithelium, whereas in the control patient there was no change. He stated also that in cases in which, owing to previous inflammation, superficial adhesions obliterated the lumen of the tube, the expansion and elongation of the tube produced by the action of the hormone could break down these adhesions and produce patency. Geist (1938) demonstrated the ability of œstrogenic hormones to stimulate rhythmic contractions of the fallopian tubes by experiments carried out on post-menopausal women.

Experiments have been carried out on these lines in 13 women, all investigations being undertaken in the Out-patient Department. Insufflation was performed on each of the 13 women, four cases showed slight patency, though in no case was tubal peristalsis present, this being regarded as the evidence of normal functioning of the tube. Two of these cases were insufflated three and one month respectively after an injection of lipiodol, when non-patency had been depicted radiographically; the former showed patency at a pressure of 130 mm. Hg, the latter at a pressure of 100 mm. Hg, thus indicating that the injection of lipiodol *per se* had a therapeutic

TABLE III.

Name	Age	Years married	Previous miscarriages or children	Husband's fertility	Diagram of lipiodol in uterus and fallopian tubes	Result of Insufflation		Tubal Contractions	Result
					normal	Before injections	After injections		
M. S.	23	2	0	+++		Non-patent at 200 mm.Hg	Non-patent	Absent	
F. M.	30	5	0	+++		Non-patent at 200	Patent at 100 mm.Hg	Good	Pregnant
G. M.	39	12	1 C aged 3	+++		Non-patent at 200	Patent at 70 (*see* Charts VII and VIII)	Good	Misc.
A. F.	24	4	0	+++		Non-patent at 200	Patent at 120	Poor	
I. W.	30	2	0	+++		Patent 3 mths. after lipiodol at 130. Contractions abs.	Patent at 90	V. fair	
L. S.	35	2½	0 B.C. ½ yr.	+++		Non-patent at 200 1 mth. after lipiodol	Patent at 100 (*see* Charts V and VI)	Good	Misc.
F. R.	30	6	1 misc. 3 yrs. ago	+++		Patent at 100. Contractions abs.	Patent at 160	Absent	
W. H.	26	6½	0	+++		Non-patent at 200	Non-patent at 200	Absent	
L. R.	36	9	0	+++		Non-patent at 200	Non-patent at 200	Absent	
D. C.	40	4	0	+	No radiograph taken	Non-patent at 200	Non-patent at 200	Absent	
V. R.	42	12	0	+		Non-patent at 200	Patent at 140-110	Good	
W. P.	29	2	0	+		Patent at 120. Contractions abs.	Patent at 100	Good	
D. M.	30	8	0	+++		Patent at 170. Contractions abs.	Patent at 70-80	Poor	
G. A.	28	5½	3 misc. induc.	++		Patent at 180. Contractions abs.	Patent at 60	Good	Only recently treated
S. C.	33	11	0	+		Patent at 190. Contractions abs.	Patent at 80	Good	Only recently treated

value. In the remaining nine cases the fallopian tubes were not patent at a pressure of 200 mm. Hg. (*See* Charts V, VI, VII, VIII.)

In 9 of the 13 patients lipiodol was injected into the uterus and in each of the 9 cases non-patency of the tubes was confirmed.

Following the above investigations, each of the 13 women received five injections of 50,000 International Benzoate Units of Œstradial Benzoate in the form of Progynon B. Oleosum Forte or Dimenformon, at five-day intervals, and at the end of the course (i.e. in most cases one month after the last insufflation and hence at a comparable time in the menstrual cycle) the insufflation was repeated.

In every case, unless otherwise stated, examination of the husband's semen showed that this was of fertility standard. Other investigations and past history did not suggest any cause other than non-patency of the fallopian tubes as the possible reason for sterility on the part of the women.

Results.—Nine of the patients in whom the tubes were non-patent, and four in whom there was slight patency, were given injections and acquired patent tubes with vigorous tubal contractions in three cases and feeble in one case. Three remained non-patent.

The three patients in whom good tubal contractions developed became pregnant, two miscarrying six weeks after the last menstrual period. (It is assumed that in these two cases an early miscarriage took place, as the missed period occurred thirty-four days after cessation of œstrin injections in the one case, and twenty-two days in the other, and in neither case had menstruation ever been more than a day or two overdue before.) One of the women who miscarried was syringing at the time as she had been fitted with a Hodge pessary.

Of the two patients in whom the tubes were shown to be non-patent on insufflation only, patency and good contractions resulted in one case. Of the four patients whose tubes were patent only at high pressure and did not show any tubal contractions, three subsequently became patent at a lower pressure and showed tubal contractions, although these were only good in one instance.

In two patients in whom patency resulted and good tubal contractions were obtained, examination of the husbands' semen showed a lowered fertility, the semen being below the standard required for successful impregnation.

It was apparent from the radiographs that the patients most likely to respond to treatment were those in whom the tubal obstruction was at the fimbrial end.

(3) *Corpus Luteum Deficiency as a Cause of Sterility*

It is known that the corpus luteum begins to function twenty-four to thirty-six hours after ovulation, and continues in the absence of fertilization of the ovum for ten to twelve days, and in the presence of fertilization, until the chorion or placenta is ready to assume the further production of hormone. As the hormone produced by the corpus luteum is responsible for the progestational proliferation of the endometrium, it can be assumed that incomplete preparation of the endometrium is due to insufficient production of progesterone (corpus luteum hormone). This may be dependent either on (1) insufficient stimulation of the œstrogenic and luteal hormones of the ovaries by the gonadotrophic hormone of the anterior pituitary, or (2) insufficient intrinsic metabolism in the corpus luteum itself.

One of the methods of determining the presence of a functioning corpus luteum is by assessing the stage of proliferation of the endometrium, fragments of which can be obtained by means of a biopsy curette. This has been done in a number of cases in which all other factors that might have accounted for sterility had been excluded, and an analysis of the husband's semen at that time showed a fertility of normal standard.

It has not been possible to obtain an estimation of the urinary output of pregnandiol.

In most cases the biopsy has been taken two days before the anticipated onset of menstruation, but the actual day of onset has been verified later by the patient and is given in Table IV.

[Sections of biopsies were shown.]

In seven patients the biopsy curettings were not compatible with the date in the menstrual cycle ; the section showed that the endometrium had not reached the late secretory stage of development. It may be argued that different parts of the uterine endometrium may show different stages of development, and that, had several curettings been taken, some might have shown a later stage ; but all these curettings have been taken from high up on the anterior wall, at which site, according to Rock and Bartlett (1937) the cytologic changes occur with consistent accuracy and progression.

TABLE IV.

Name	Age	Years married	Menstrual cycle	Comments	Day of biopsy before menstruation	Stage of endometrial development	Treatment given	Pregnant
V. R.	42	12	2-4 / 28	Scant menstrual loss	2	22nd–23rd	None	
D. S.	31	5	4-5 / 24	Often one day's intermenstrual bleeding	2	18th–19th	Œstradiol benzoate 20,000 I.B.U. 9th day of cycle, oral progesterone 5 mgm. 5 times in 10 days preceding menstruation	
E. P.	34	4½	4 / 28	Menstruation delayed twice 2 weeks and 4 weeks	2	18th–19th	As above	Now 4½ months
A. R.	33	4½	5 / 24		1	19th–20th	3 injections of 5 mgm. corpus luteum hormone in the 10 days preceding menstruation. Pregnant after 2nd month treatment	Miscarried at 3 mths.
L. P.	30	7	4-5 / 24	Once menstruation delayed 2 weeks	2	16th–17th	4 injections of 5 mgm. corpus luteum in the 10 days preceding menstruation	
G. E.	28	2½	3-4 / 26-27		2	23rd–24th	Follicular hormone 50,000 I.B.U. 10th day of cycle, 3 injections of C.L. hormone in the 10 days preceding menstruation	
J. H.	24	5	6 / 26		1	21st–22nd	As above	? pregnant. 3 weeks overdue (*see* text)

On looking at the table it will be seen that in five instances the patient gave a history of a short menstrual cycle ; in one case there was also a one day's intermenstrual loss (ovular bleeding), and in another case menstruation had been delayed for two weeks on one occasion, suggestive of failure of implantation of a fertilized ovum. In a sixth case menstruation had been delayed for two weeks on one occasion and for four weeks on another.

Now ovular bleeding has been noted by many observers (e.g. Hartman, 1932 ; Hain, 1934) and is probably due to a disturbance of the hormonal equilibrium at the time of ovulation, resulting in diminished endometrial stimulation sufficient to induce partial disintegration of the endometrium and slight uterine bleeding. As corpus

luteum hormone is mobilized, the endometrial stimulation is restored and bleeding ceases. Macgregor (1938) has demonstrated arrest of intermenstrual bleeding on administration of corpus luteum hormone, and in several patients I have also succeeded in eliminating this symptom.

When menstruation on an occasional instance has been two or three weeks overdue and premenstrual curettage has yielded evidence of progesterone deficiency, it is probable that nidation had occurred, and there had been insufficient hormone produced to meet the demands of progressive development, so that an early abortion had taken place. The subsequent history of one of the patients appears to confirm this supposition.

It seems then that in six out of the seven patients the history suggested a lowered function of the corpus luteum, and since Venning and Browne (1937) have noted that where the luteal phase is short functional sterility exists, these were obviously cases which might benefit from administration of corpus luteum hormone.

Corpus luteum hormone was given to six out of the seven patients in whom endometrial biopsy revealed that the degree of progestational proliferation did not harmonize with the date.

Inability of the patient to attend Out-patients or to pay her own doctor for the injections, although the material was supplied, prevented the administration of corpus luteum hormone during the last ten days of each menstrual cycle. One patient did not undergo treatment. Two patients were given injections of corpus luteum hormone of 5 mgm. each, three times in the ten days preceding menstruation, and one became pregnant after the second month's treatment though unfortunately she miscarried at three months' gestation ; she had received corpus luteum injections from her own doctor, but not in sufficient quantity to combat her deficiency.

In two cases an injection of 50,000 International Benzoate Units of follicular hormone given on the tenth day of the shortened cycle preceded the corpus luteum injection. One of these patients, when last heard of, was three weeks overdue with her menstrual period, but she became an evacuee at the beginning of the war, and I have failed to trace her since.

Two other patients were given œstradiol benzoate of 20,000 International Benzoate Units on the tenth day of the cycle followed by the oral administration of five tablets of crystalline progesterone, each of 5 mgm. in the ten days preceding menstruation, one became pregnant at once and is now at four months' gestation. Hamblen *et al.* (1939) carried out a series of experiments to show that crystalline progesterone was inefficiently utilized, but Venning and Browne (1938) state that the effect was better if œstrogen and progesterone were both given. I suggest, however, that even if the crystalline preparation is inefficiently utilized, it may suffice to stimulate the intrinsic metabolism of the corpus luteum in some way, though Hamblen failed to note an increased output of pregnandiol complex in the urine.

Some of the patients stated that while undergoing treatment the menstrual cycle was prolonged to twenty-eight days.

Summary

I.—A comparison has been made between uterosalpingography and tubal insufflation, and the relative diagnostic and therapeutic values of each discussed. It is claimed that lipiodol injection has a higher therapeutic value and that tubal insufflation affords a better means of diagnosis.

II.—161 patients were given lipiodol injections ; 28·3% of the total became pregnant, and 47·3% of those in whom there was no obvious cause for infertility in either husband or wife. The corresponding figures in 48 insufflations were 10·4% and 25%.

III.—The effect of follicular hormone in non-patent fallopian tubes was demonstrated in nine cases, and on tubes showing partial patency and absence of peristalsis in four cases. In nine instances patency resulted, tubal contractions were obtained in eight, poor in two instances. There was no improvement in four cases, three patients became pregnant, though two miscarried.

IV.—In seven patients who had remained sterile after exclusion of other known possible factors, sections of endometrial biopsies showed evidence of corpus luteum deficiency. This deficiency was supplemented in six cases, two patients definitely became pregnant, and a third probably became pregnant; the latter, however, has been lost trace of. One miscarried.

I am much indebted to Miss Dearnley who has allowed me to carry out these investigations in her Out-patient Department, and I am grateful to Roussel Laboratories who have kindly supplied me with corpus luteum hormone—Lutogyl.

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Miss Moore White's paper was discussed by Mr. Vartan and Mr. Green-Armytage.

A Case of Congenital Abnormality of the Uterus.—A. BRIANT EVANS, F.R.C.S.

Case history.—The patient was first seen in October 1936, at the age of 19, when she was admitted to the Chelsea Hospital for Women on account of recurring hypogastric pain and primary amenorrhœa. The pains of which she complained occurred each month and usually lasted for three or four days and were gripping in character. There was no menstrual flow but frequency of micturition and occasionally diarrhœa. No family history of any similar lesion.

The patient was an attractive young girl, with the breasts and other secondary sexual characteristics well developed. Examination under anæsthetic showed that the external genitalia were normal, but the vagina was only 1 in. in length and terminated blindly, corresponding to that part below the level of the hymen developed from the urogenital sinus. On rectal examination the ovaries appeared to be normal, a rudimentary stump of uterus could be felt, but there was no true vagina.

The conclusion reached was that the patient had a rudimentary uterus with periodic attempts at menstruation.

She was readmitted in January 1940 on account of abdominal pain. Seven months prior to admission she had had a sudden attack of lower abdominal pain, localized to the right iliac fossa and accompanied by nausea. Since that time she has had an almost continuous nagging pain in the right iliac fossa. This pain was quite different in character to the cyclical pains, from which she still suffered.

She had been married in July 1938, and intercourse had proved to be perfectly satisfactory.

Abdominal examination showed some cæcal distension and tenderness over McBurney's point. The vagina was now 2½ in. in length and admitted two fingers.

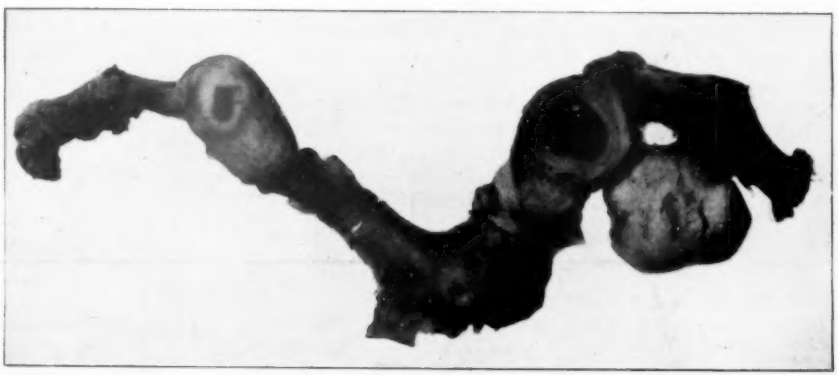
A diagnosis was made of chronic appendicitis and congenital deformity of the uterus.

Operation.—By Mr. Rivett on January 26, 1940, under general anæsthesia with continuous evipan.

A transverse suprapubic skin incision was made and the rectus sheath and peritoneum opened in the mid-line. There was no uterus in the normal position, but the Müllerian ducts could be seen converging behind the bladder. The ovaries and fallopian tubes were normal but, at the junction of the fallopian tubes with the Müllerian ducts, were two small uterine bodies. The pouch of Douglas contained a small amount of dark menstrual blood. The appendix showed signs of chronic inflammation, being thickened and enlarged.

The Müllerian structures were excised together with the left ovary, leaving the right ovary intact. This was done to relieve the patient of her cyclical symptoms, due to cryptomenorrhœa, and to allow of a histological examination of the abnormality. Appendicectomy was performed and the abdomen closed.

Post-operative convalescence.—The patient made an uncomplicated post-operative recovery. She was last seen one week ago, free from symptoms with the abdominal incision well healed.



A photograph of the specimen taken after its removal. It shows the left ovary, fallopian tubes, uterine bodies and the caudal portions of the Müllerian ducts converging together. The cavities of the uterine bodies and the lumina of the fallopian tubes were full of blood, *i.e.* bilateral hæmatometra and hæmatosalpinx. Sections showed this condition.

Conclusion

The specimen demonstrates failure of development of the lower part of the Müllerian system and, morphologically, somewhat resembles the twin uteri of marsupial mammals. I do not know how rare the condition is, but I imagine that similar abnormalities would be found in other cases of congenital absence of the vagina, if they were submitted to laparotomy.

On looking up the records of eight cases of congenital absence of the vagina, which have been admitted to the Chelsea Hospital for Women during the past three years, only one had cyclical abdominal pain and at laparotomy was found to have a hæmatometra. It would, therefore, appear that this symptom is due to the presence of functionally active endometrium.

I should like to express my thanks to Mr. Rivett for permission to show his specimen to the Society, and to Mr. Barton Gilbert for his expert opinion on the microscopical slides.

This case was discussed by Mr. Gordon Luker and Dr. Martindale.

Mr. Green-Armytage showed a film demonstrating his technique for "Vaginal Hysterectomy" which was discussed by Mr. Hedley, Mr. L. Phillips, Mr. McCurrich, Mr. Miles Phillips, Dr. Fletcher Shaw, and Dr. Chassar Moir.

Section of Orthopædics

President—T. P. McMurray, M.Ch.

[*March* 5, 1940]

Meeting Held at the Royal National Orthopædic Hospital, London.

Protrusio Acetabuli.—A. Rocyn Jones, F.R.C.S.

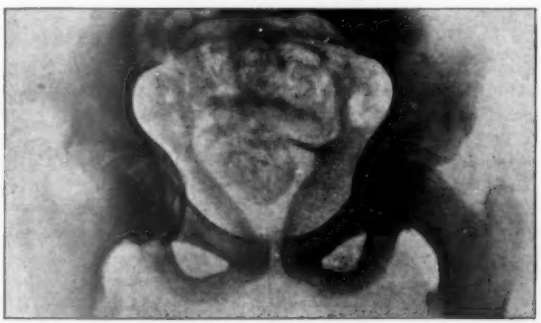
S. T., female, aged 12½ years. First came to hospital in 1938, giving a history of pain in the right hip, and hardly able to walk.

On examination.—Movements at each hip greatly restricted; flexion of the right hip 10°, of the left 5°. Abduction of the right hip 15°, left 20°. Adduction nil. Internal and external rotation nil. With standing, the lumbar lordosis was exaggerated.

Radiographs revealed unusually deep acetabula, the floors of which projected into the pelvis—a condition known as protrusio acetabuli (Otto's disease).

For several months the child had recumbent treatment, with the lower limbs in abduction, with 9½ lb. traction to the left lower limb, and 8½ lb. to the right, and with the foot of the bed raised. On 12.7.39 her hips were submitted to a manipulation. It was possible under the anæsthetic to increase the movement of each hip in every direction.

The child has been able to get about much more easily, and all pain has disappeared from the right hip. Movements of abduction and flexion of the hips are still greatly restricted.



Radiograph of a female child aged 12½.

A case of protrusio acetabuli. First came under observation at the age of 12½. The acetabula project somewhat deeply into the pelvis; the joint space is well preserved in each hip and there is no evidence of arthritic changes.

Tuberculosis of the Gluteal Bursa.—V. H. Ellis, F.R.C.S.

Tuberculosis of the great trochanter of the femur may arise in two ways: hæmatogenous infection of the bone, and extension to the bone from the overlying gluteal bursa. In children the first is more frequent, in adults the second. The appearance of the two conditions is dissimilar radiologically. In tuberculosis of the gluteal bursa there is absorption of the trochanter without the signs of tuberculous disease, i.e. general rarefaction, a woolly outline, and increased differentiation between cortex and deeper bone.

In this case the patient had a gluteal bursa full of old caseous material, but there was no evidence histologically of tuberculous invasion of the bone, old or recent, except for one miliary tubercle in the tip of the trochanter. The absorption of bone must therefore be due to mechanical causes. The variation in pressure within the bursa due to the activity of the overlying gluteal muscles produced an osseous reaction analogous to that occurring in vertebral bodies in contact with an aortic aneurysm or with the "aneurysm phenomenon" in dorsal spinal caries.[1]

[1]Ghormley, R. K., and Bradley, J. I., *J. Bone & Joint Surg.*, 1928, **10**, 796.

Congenital Dislocation of Left Hip. Perthes' Disease of Right Hip.—A. T. Fripp, F.R.C.S.

M. J., female, aged 7 years.

History.—First seen in February 1938, when the mother said that she had noticed a limp on the right leg for some weeks. Apparently no abnormality due to the left hip had been noticed.

On examination.—Waddling gait, which was more marked to the right than to the left. Radiographs showed congenital dislocation of the left hip and advanced Perthes' disease of the right hip.

Extension was applied to the left leg for three weeks and the dislocation then reduced by manipulation.

FIG. 1.

FIG. 2.

She is now walking in a patten-ended caliper on the right leg. X-rays show satisfactory position of the left hip and regeneration of the right hip, with considerable flattening of the head of the femur.

Radiographs.—Original condition (fig. 1). Present condition (fig. 2).

Hyperparathyroidism in a Patient with Infantile Coxa Vara.—A. T. FRIPP, F.R.C.S.

W. W., male, aged 29.

History.—When aged 8 years he had an operation (? subtrochanteric osteotomy) in the region of the right hip. For the last twelve years he had noticed gradually increasing genu valgum.

On examination.—He walked badly, with a waddling gait. The great trochanter was raised on both sides and flexion and abduction of the hips were limited. There was 5 in. of knock knee.

Investigations.—X-rays of skeleton: some alteration in the calcium content of bones which is unequally distributed; coarse trabeculation of fairly dense texture.

Doubtful cyst in the tibia. Well-marked coxa vara of both hips, of the infantile type, and genu valgum.

Blood-calcium ranged between 13·6 and 15·6 mgm. per 100 c.c. Calcium balance: Period I: intake 0·25 grm., output 1·27 grm. Period II: intake 0·26 grm., output 0·97 grm. Blood phosphates: 2·3 mgm. per 100 c.c. Phosphatase: 6, 8, 9, and 14 units on different days. Wassermann reaction negative. Blood-count normal.

Operation, 15.6.39 (Mr. R. Vaughan Hudson).—A cyst of the parathyroid weighing 1 grm. was found outside the thyroid sheath on the right-hand side. Two hours after

X-ray of right hip showing infantile type of coxa vara with old subtrochanteric osteotomy.

operation the blood-calcium had fallen from 15 to 14·3 mgm. per 100 c.c. and later it fell to 9·6 mgm. per 100 c.c. and tetany was seen. Calcium was given and it became steady at 10·8 mgm. per 100 c.c.

Pathological report (Dr. R. W. Scarff): Section shows tumour composed of parathyroid tissue. There are areas indicative of glandular activity.

12.12.39: Blood-calcium 10·6 mgm. per 100 c.c. 17.1.40: Blood-calcium 11·5 mgm. per 100 c.c. Blood phosphates 3·6 mgm. per 100 c.c. Phosphatase 6·6 units. 12.1.40: Bilateral osteotomy of lower end of femur. The bone was still abnormally soft.

I am indebted to Mr. Vaughan Hudson and to the Middlesex Hospital for an account of the operation findings.

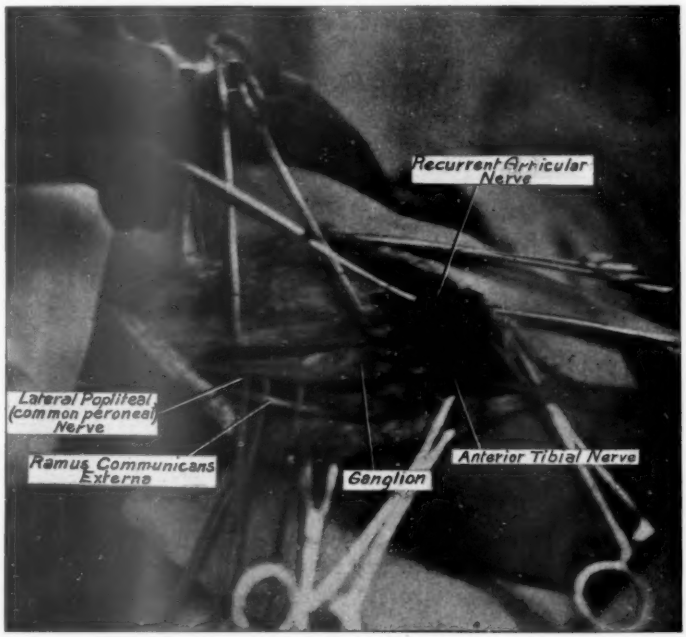
A Case of Ganglion in the Sheath of the Lateral Popliteal (Common Peroneal) Nerve.—H. E. Harding, F.R.C.S.

A. D., aged 33. Occupation, clerk.

Complaint was made of attacks of pain on the dorsum and outer side of the right foot together with progressive weakness of the foot. The symptoms had lasted for about a month and were not associated with any definite injury or other cause.

Examination showed that there was relative anæsthesia and analgesia over the skin area supplied by the lateral popliteal (common peroneal) nerve, inability to dorsiflex but not to evert the foot; and in the line of the nerve, from the neck of the fibula upwards along the biceps femoris tendon, was an elongated tender cystic swelling. Pressure on the swelling caused pain on the dorsum of the foot. X-ray examination of the knee showed slight osteo-arthritic changes. The anterior tibial group of muscles responded to galvanism but not faradism; the peroneal muscles responded normally.

The lateral popliteal nerve was explored six months after the onset of symptoms. The nerve was normal above the level of the ramus communicans externa but below this level was expanded and loculated. This change extended along the recurrent geniculate branch but not into the other terminal branches. The sheath of the nerve was incised and a multilocular ganglion dissected out. Electrical stimulation of the nerve above and below the lesion both before and after removal of the ganglion produced the same response as formerly.



The pathologist reported an endothelium-lined cyst without neural elements.

The wound healed well, sensation returned to normal a few days later, and by the end of a further two months the foot could be held in mid-dorsiflexion. Nine months later, apart from slight weakness of extension in the toes, recovery is complete and there is no sign of local recurrence.

(Two other cases of this condition, previously reported[1] were also shown.)

[1]Ellis, V. H., *Brit. J. Surg.*, 1936, **24**, 141.

The following cases were also shown :—

By A. Rocyn Jones, F.R.C.S.

Tendon Transplant for Irrecoverable Musculo-spiral (Radial) Nerve Paralysis from Gunshot Injury. Operation in 1918. Almost full function of hand restored.

By V. H. Ellis, F.R.C.S.

Amputation Through the Hip-joint for Arthritis with Vascular Complications.

By A. T. Fripp, F.R.C.S.

Congenital Lateral Displacement of Patella.

By K. I. Nissen, M.D., F.R.C.S.

Calcification of Organized Exudate in the Knee-joint.

Subcutaneous Prepatellar Calcification.

Synovial Chondromatosis of Knee.

Calcification in Area of Traumatic Necrosis of Infrapatellar Pad of Fat.

Osteochondritis Dissecans of Knee.

Osteochondritis Dissecans of the Outer Femoral Condyle.

Brodie's Abscess of Patella.

Brodie's Abscess of Femur.

By E. H. Hambly, F.R.C.S.

Severe Rickets of Unknown Origin in Adolescence.

? Delayed Active Rickets.

Renal Rickets.

By S. L. Higgs, F.R.C.S.

Complications following Nail Arthrodesis of the Hip-joint.

Radiographs of the following were demonstrated :—

By S. L. Higgs, F.R.C.S.

Lambrinudi's Method of Treatment of Fractures with Intramedullary Kirschner Wire [Lambrinudi, C., *Proc. Roy. Soc. Med.*, 1940, **33**, 153 (Section of Orthopædics, p. 17)].

By F. Campbell Golding, M.R.C.P., D.M.R.E.

Examples of Syphilis of Bone.

Protrusion of Intervertebral Discs.

JOINT DISCUSSION No. 2.

Section of Medicine and Section of Surgery

Chairman—Sir Maurice Cassidy, K.C.V.O., M.D.
(President of the Section of Medicine)

[*February* 27, 1940]

DISCUSSION ON THE SURGICAL TREATMENT OF ANGINA PECTORIS

Dr. Geoffrey Bourne : In no other branch of clinical medicine is diagnosis more often difficult than in patients suffering from cardiac pain. Here is an account of three patients I have seen.

A man aged 54 suffered from severe pain in the chest which was of two types, acute attacks lasting for a comparatively brief period, and a constant pain which might last for hours at a time. The pain was increased after exertion and after emotion. He was told that he was suffering from " angina pectoris ". Since that time, three years ago, he had done no work. On examining him at St. Bartholomew's Hospital I found that the pain was left-sided, that it was so severe that he was afraid to walk, and his limit seemed to be about 100 yards ; but on careful questioning it was evident that the pain did not vary with the degree of exertion, nor did it diminish when the exertion ceased. It might last for some hours subsequently. My opinion that the pain was of the functional type was borne out by a full clinical, electro-cardiographic, and radiological examination. I then sent him to a psychiatrist. Within a month the pain had disappeared. He has since resumed full work as a parquet floor layer, at which he has continued for a period of two years up to the present time.

The second case was a man aged 58. I had seen him two years previously, and had come to the conclusion—again after full examination—that the pain was functional and not of coronary origin. At the time of the second admission to St. Bartholomew's he was treated by alcohol injection, and his previous pain became worse. When I myself saw him subsequently it was still clear that the pain was not coronary in type.

The third case was similar ; he had been treated by sympathectomy. I refused to consider the question of thyroidectomy, which was the point at issue. A psychologist found an advanced degree of obsessional neurosis.

In a ten-years' follow-up investigation of cardiac pain I have met with a number of similar cases. Since diagnosis may thus be difficult for physicians of experience, it is clear that no surgeon should consider treating patients with severe cardiac pain, trusting in his own powers of diagnosis. Statistics of results are not worth publication unless the original diagnosis has been made with extreme care.

No case should be regarded as being suitable investigative material unless classical angina of effort is present. In this condition the pain is strictly quantitative to the degree of exertion undergone. It is increased during exercise, and diminishes as

soon as the patient rests. The question " does exercise make the pain worse ? " is an insufficient question, the point being whether pain is brought on during exercise, not whether pain is produced after exercise ; and further, whether the pain diminishes during rest, or whether it is still felt for a period of possibly hours, although the patient is at rest. Other helpful points are the central position of the pain, relief by nitroglycerin, absence of superficial hyperæsthesia over the chest wall, and changes in the electrocardiogram indicating coronary disease. Here again it must be remembered that the presence of organic coronary disease is of itself not exclusive of a functional type of pain. This functional pain, which is sometimes known as left mammary pain, pseudo-angina, or as I have somewhat provocatively named it, angina innocens, may follow a coronary thrombosis, although, of course, angina of effort is the usual sequel in this case.

Angina of effort indicates insufficient coronary dilatation during exercise, or rigidity or narrowing of the coronary vessels also appearing during exercise.

In angina of effort, the more full the information the higher is the percentage of patients found to have coronary disease. Dr. Bodley Scott and I (*Brit. M. J.*, 1938 (i), 55) in 112 cases of angina of effort, strictly chosen, found only 13 in whom evidence of cardiovascular disease was absent. In a subsequent electrocardiographic investigation Dr. Courtenay Evans and I, also in classical angina of effort (*Lancet*, 1938 (ii). 1354) found in a series of 80 cases no change in the electrocardiogram, in Leads 1, 2, 3, and 4, in 30% of cases. Subsequent examination of these negative cases, by means of exercise or exposure to a temperature of 10% or 12% oxygen, has reduced the percentage of negative cases to about 20%. A number of papers on the post-mortem appearances in cases of angina of effort corroborate this position.

Surgical measures are undertaken for two objects in this condition, relief of pain, and revascularization.

J. C. White, in a long series of patients treated by alcohol injection, concludes that the analgesia produced is harmless, and my own series of 15 cases, treated by thyroidectomy, corroborates his conclusion. Exercise should benefit the hypertrophy and health of the remaining muscle fibres, and should stimulate the re-canalization of thrombosed vessels, and help also to induce re-vascularization of an area previously partially deprived of its blood supply.

My experience of sympathectomy has not been particularly favourable, but, with the newer methods introduced by Professor Ross and others, this opinion will probably need to be revised.

Alcohol injection is attended by the minor accidents of partial pneumothorax and local pleurisy, and by the more unpleasant alcohol neuritis in a few cases.

Thyroidectomy is the surgical measure of which I personally have had most experience. The prominence I give to it here is due to this fact alone. The series of cases which I am showing seem to indicate that thyroidectomy definitely has a place in the treatment of severe cases of anginal pain (Geoffrey Bourne and J. Paterson Ross, *Lancet*, 1938 (ii), 815 ; *St. Barth. Hosp. Reports*, 1938, 71, 61).

The mode of action of this measure is explained by three different hypotheses. Firstly, it is said to decrease the blood-flow, secondly it is said to be due to injury of the nerve plexuses placed behind the thyroid at the time of operation, and thirdly, it may decrease the sensitivity either of the visceral sensory nerve-endings or of the motor nerve-endings in the coronary vessels. The first of these hypotheses would not appear to stand critical analysis. A patient has very severe pain on walking across a room, dressing, or on experiencing very slight emotion. After thyroidectomy the same patient can carry a suitcase to the station, or can bicycle for 20 miles without pain. Is it conceivable that thyroidectomy has kept the coronary rate of

blood-flow during these exercises below that which previously was produced by dressing? If not, some other factor must obviously be postulated. Injury to the retrothyroid ganglia was first considered by A. A. Weinstein and H. Hoff (*Surg. Gynæc. and Obstet.*, 1937, **64**, 165), but this does not explain the following observed facts in two of my cases. These two patients were relieved of their pain by thyroidectomy. If they subsequently took too much thyroid extract the pain would return after a lapse of two or three days. When they stopped the thyroid extract, the pain would persist for a further two or three days and would then subside. This would seem to indicate that thyroxin has some visceral sensitizing effect on pain. In my experience thyroidectomy is disappointing in the treatment of congestive failure, but in very carefully chosen cases it is extremely successful in severe angina of effort, whether this condition is complicated by attacks of spasmodic angina or not.

The results are seen in the table.

15 Cases of Very Severe Pain Chosen from about 400 Cases of Angina of Effort (some had Spasmodic Attacks also).

Case, Sex Age at time of Operation	Pre-Operative Course	Alive or Dead	Post-Operative Course			
			Duration	Relief	Result Good, Fair Bad	Remarks
(1) M. 48	2 yrs.	A.	4 yrs.	Complete 1 yr. then very slight pain	G.	Cor. infarct 20 m. after operation
(2) M. 60	2 yrs. 6 m.	A.	3 yrs. 7 m.	Complete 2 yrs. Partial since	G.	Climbed steeples after
(3) M. 47	7 yrs. 6 m.	D.	2 yrs. 3 m.	Complete 9 m. Partial since	G.	Cycled 25 miles daily till 2 m. before sudden death
(4) F. 59	7 yrs. 6 m.	D.	2 yrs. 9 m.	Complete	G.	Previously bedridden with pain. Normal life after
(5) M. 64	9 yrs.	D.	7 m.	Not much relieved	B.	Died of coronary infarction
(6) M. 48	4 yrs.	A.	2 yrs. 2 m.	Complete	G.	Works hard as silversmith
(7) M. 73	8 yrs.	D.	1 yr. 4 m.	Complete for 6 m. Pain returned	F.	Note age at time of operation
(8) F. 55	3 yrs.	A.	2 yrs. 4 m.	Complete	G.	Walks well and works in garden.
(9) M. 55	5 yrs.	A.	1 yr. 3 m.	Complete for 1 yr. Slight recurrence	G.	
(10) M. 68	3 yrs.	A.	1 yr. 3 m.	Complete for 2 m. then relapse	B.	
(11) F. 63	2 yrs.	A.	1 yr. 4 m.	Complete	G.	Bedridden with pain before
(12) M. 67	8 yrs.	D.	3 weeks	Complete	G.	Died at stool. P.M. showed both coronaries grossly diseased
(13) M. 57	7 yrs.	A.	1 yr. 6 m.	Nearly complete. Very occasional pain hurrying	G.	
(14) M. 67	3 yrs.	A.	1 yr. 2 m.	Complete for 1 yr. Pain on hurrying lately	F.	Previously bedridden. Walked 2 miles a day till recently
(15) F. 18	1 yr.	A.	1 yr. 3 m.	Complete	G.	Extreme aortic incompetence (rheumatic). Pain previously on slightest exertion

Points worth noting are the duration of the successful post-operative course, the amount of exercise freely taken during this time, the age of patient No. 7 at the time

of operation, and the fact that patient No. 12 proved a good operative risk, although the post-mortem three weeks later showed that both coronaries were grossly diseased. This patient also had a bundle branch lesion. His pain, however, was so extreme that the operation was done with full knowledge that the heart was extremely diseased.

The indications for thyroidectomy are: The diagnosis is certain. The pain is very severe and shows no sign of diminution after a sufficient spell of treatment by other means. No recent coronary infarction shall have occurred, for angina of effort following this is apt to disappear spontaneously.

The chief contra-indications are: Adiposity, a visibly progressive cardiac lesion, advanced myocardial degeneration, and the presence of severe renal or other disease.

The post-operative treatment comprises rest in bed for three to five weeks. No thyroid is given until slight signs of myxœdema, such as increase in weight, slight lethargy and sensitivity to cold begin to appear, then sufficient thyroid extract to remove these slight symptoms is given, the usual dose amounting to about gr. $\frac{1}{2}$ four to six times per week.

Revascularization operations have been a matter of practical politics since the work of Beck (Beck, C. S., *Surg., Gyn. and Obstet.*, 1937, **64**, 270) and O'Shaughnessy (D. T. D. Davies, H. E. Mansell, L. O'Shaughnessy, *Lancet*, 1938 (i), 76). Does revascularization occur in man as a result of such surgical operations? What is the post-mortem evidence?

Of five cases, done at St. Bartholomew's Hospital, one died immediately after the operation, and a second one year and four months after. The latter had suffered from practically no pain since the operation but had complained of increasing dyspnœa. At post-mortem the investigation showed no evidence of revascularization. Of the other three cases, one stated that the pain was 75% better but still complained of dyspnœa, one states that the pain is now very slight and that he can walk two miles at a moderate pace, and the fifth case walks normally and is well two years and six months after the operation.

The following pathological considerations are important:—

Attention should be focused upon the state of the recipient muscle. Angina of effort of a severe degree indicates coronary disease with living muscle fibres beyond, which are periodically starved of their blood supply. This would seem to provide a fertile field for revascularization. Previous coronary infarction, and *a fortiori* several such infarctions, would seem to be a less good indication for this form of treatment. Fibrous tissue is not a good or a useful recipient, if it is a possible one. The field would here seem to be extremely stony. It is conceivable in future that electrocardiographic investigation of patients by exercise or with anoxæmia might bring out cardiographic changes due to coronary disease which would enable us to diagnose the position of the anoxæmic area, whether anterior or posterior. It would seem that omentopexy of the left ventricle might not be useful if the posterior coronary circulation is the one causing symptoms. Although revascularization is obviously the most scientific form of surgical approach to the problem, in view of the many difficulties existing at present, it would seem that the relief of cardiac pain of a coronary type is best achieved either by thyroidectomy or by alcohol injection, in the hands of an expert.

Professor J. Paterson Ross: *Revascularization of the myocardium.*—Angina of effort may be likened to the limb pain of intermittent claudication, the reason for both being found in the relative ischæmia of a working muscle. Disease of the coronary arteries having produced an obstacle to the free passage of blood

to the heart muscle, the ideal treatment would appear to be the provision of a fresh blood supply.

It is for this reason that I place the operations of muscle grafting or omental grafting first among the surgical procedures for the relief of angina. The function of the omentum in providing a blood supply to infarcted portions of abdominal viscera is well known ; cases in which I have observed this phenomenon lead me to suppose that the operation of cardio-omentopexy has a sound theoretical foundation.

Total thyroidectomy.—The surgeon who wishes to remove every trace of thyroid tissue must be concerned about the preservation of the recurrent laryngeal nerves. No doubt the ideal method would be to display the nerve in every case, for by seeing it clearly it may be avoided, whether it runs anterior or posterior to the inferior thyroid artery ; and whether it is separated from the gland by a dense sheet of fascia, or runs, as it occasionally does, not only in close contact with but actually through the substance of the lateral lobe. I have preferred, however, to work carefully round the side of the lobe, keeping as close as possible to the capsule of the gland and stripping the fascial sheath off its surface, clipping all the branches of the vessels with mosquito forceps, and I have thus avoided injuring the nerve. Though it has frequently been seen it has not been exposed deliberately before removing the lobe.

This method may be rather more tedious than primary ligation of the inferior thyroid artery, exposure of the recurrent nerve, and subsequent excision of the gland, but it has the advantage of leaving the tissue outside the fascial sheath almost undisturbed. This is a matter of practical importance in avoiding injury to the parathyroid bodies, and of theoretical interest in that the damage to any of the sympathetic nerve-fibres which run close behind the gland must be minimal. The relief of pain after this operation has been just as striking and has occurred just as early as in cases recorded by other surgeons, which seems to refute the suggestion that thyroidectomy is effective not because thyroid tissue has been excised, but because sympathetic nerves have been severed.

Acting upon this suggestion, some of the Edinburgh surgeons have removed only the lateral lobes, leaving the isthmus to supply the thyroxin-requirements of the body, thus avoiding the necessity for post-operative thyroid medication. It will be interesting to hear the late results of their cases, but while not denying the existence of sympathetic fibres close behind the gland, it is hard to believe that the incidental damage to these nerves in the course of removal of the thyroid would give better results than the deliberate excision of the cervical sympathetic trunk and its cardiac branches.

The thyroxin factor must be important, since the administration of thyroid substance after the operation must be very carefully controlled to avoid the recurrence of pain which follows an overdose. It is quite likely that it may not be thyroxin itself which is directly responsible for the pain—it may be that its effect comes from sensitizing the tissues to circulating adrenaline—but in my opinion there is good reason to insist upon complete removal of the thyroid gland. Any tendency to myxœdema is easily controlled and patients are able to lead active and useful lives after the operation.

Sympathectomy.—Physiologists are not yet in entire agreement as to the functions of the complex sympathetic cardiac nerves. There is no doubt that they convey accelerator impulses, and the balance of the evidence is in favour of their being dilator nerves to the coronary arteries. The French and some American physiologists, however, believe that they convey vasoconstrictor impulses to these vessels, and Leriche sees in the stellate ganglion a reflex centre receiving afferent impulses from the heart and aorta which produce a pressor response resulting in a quickened heart beat and coronary constriction. Upon this conception he bases his argument

for stellate ganglionectomy, believing that the beneficial effect is due to the blocking of efferent rather than afferent impulses.

Here we favour the view that sympathectomy is beneficial because in dividing the sympathetic nerves we must also cut the visceral sensory fibres which accompany them, our object being, in fact, sensory denervation and not sympathectomy, except in so far as slowing the heart rate may be a relief to the under-nourished muscle.

Stellate ganglionectomy will block a large proportion of the afferent nerve-fibres from the heart, but as pain fibres enter the spinal nerves along the white rami of the upper four or five thoracic nerves complete sensory denervation involves a very extensive operation. Although it is often possible to reach as low as the 4th thoracic ganglion by the anterior approach to the cervicothoracic portion of the sympathetic chain, this may prove to be rather an extensive operation for a patient with heart disease, and therefore the alternative of alcohol injection has to be considered.

The correct placement of the alcohol can be shown (at the upper end of the injection area at all events) by signs of sympathetic paralysis, and, given a reasonable amount of practice, the method should be accurate enough to achieve its object. It has the drawback, however, that intercostal neuritis is a sequel which can hardly be avoided since the alcohol must affect the intercostal nerves as well as the rami communicantes. I would therefore prefer to excise the sympathetic trunk whenever the patient's condition permits it.

The risks of surgical intervention.—The majority of patients with angina stand the strain of operation surprisingly well. This strain can be reduced to the lowest possible limit by avoiding emotional excitement before the operation starts, and venous congestion during anæsthesia.

Cardio-omentopexy is to be regarded as a more formidable procedure than either sympathectomy or thyroidectomy ; alcohol injection may be undertaken when the latter operations are contra-indicated ; but whereas convalescence from either of these is likely to be uneventful, the neuritis following alcohol injection may prove to be a severe tax upon the patient's endurance.

The risk of sudden death after the patient has been deprived of his painful " danger-signal " has been over-stressed in the past. Many of our patients have observed a peculiar but painless sensation in the chest which still acts as a warning, but the improvement which occurs in the patient's general condition when he no longer suffers frequent attacks of severe pain more than compensates for the risk of over-straining an insensitive heart, and the increased exercise which the operation has permitted may even improve the nutrition of the myocardium as well as the state of the body as a whole.

As far as we know, sympathectomy merely blocks sensory impulses—the heart is exposed to the same strain as before but pain is not felt. The aim of thyroidectomy is to spare the heart by diminishing the work it has to do, and thus to avoid the effort which produces the pain.

Mr. A. Dickson Wright : Angina pectoris can be grouped into two classes :—

(1) Spurious cases in which the disease is simulated by neurotics or by other diseases like cholecystitis, pleurodynia, diaphragmatic hernia, &c.

(2) True cases : (*a*) With the heart functioning well in all other respects, these cases are often cured by some other event such as an emergency operation or major illness.

(*b*) With signs of heart dysfunction either primary or secondary to cholecystitis,

hyperpiesia, goitre, aneurism and tachycardia of the paroxysmal and effort syndrome types.

The surgical approach to angina is not much employed in this country because in a disease so associated with sudden death the physician tends to exclude the surgeon lest his ministrations should coincide with this event; also the patient under the shadow of heart disease shuns the operation though possibly not so much as his dependants who do not suffer the pain.

Surgical Treatment

Secondary angina.—(*a*) Gall-bladder disease should be eradicated; quite dramatic results are obtained in this group.

(*b*) Hypertensive cases. If there are definite signs that the blood-pressure is labile and kidneys are undamaged, splanchnic and lumbar ganglionic resection is indicated. In a series of 32 of these cases I have had three with angina and they have all benefited by operation.

(*c*) Paroxysmal tachycardia can be cured by operations on the upper five thoracic ganglia on the right side, and associated angina disappears with the tachycardia.

(*d*) Effort syndrome. There may be some hope in this almost hopeless malady by disconnecting the heart from its badly behaving accelerator nerves.

(*e*) Aortic aneurism. In two cases I have anastomosed external carotid and external jugular and the resulting drop in blood-pressure has helped the pain.

Primary angina.—The surgical method of attack may take several forms:—

(*a*) Division of the sympathetic nerves of the heart. It is probable that this operation not only stops the pain but also helps the heart by reducing vasoconstriction of the coronary arteries and by eliminating pressor and accelerator impulses carried by these nerves. In a disease checked so magically by vasodilator drugs there is hope in an attack upon the vasoconstrictor nerves. The operation to relieve pain is directed towards the upper thoracic ganglia on the *left* side. The large published mortality from this operation is out of date and applies to the posterior mediastinal approach. There is practically no mortality in the safe anterior approach designed by Paterson Ross.

(*b*) Alcohol injection of the upper five dorsal ganglia on the left side in the hands of White produces remarkable results. My own feeling is to restrict this to cases with heart failure and employ the operation with its greater precision upon the less ill patients.

The criticism made against these operations on the nerves of the heart is twofold. Firstly the removal of the pain is stated to remove a valuable inhibition, saving the patient from excessive effort. The answer to this is that there are other sensations which will still check the patient after operation such as epigastric or right-sided discomfort and dyspnœa. The second objection is that by denerving the heart valuable stimuli to the heart are lost and its effort cannot be mobilized when required. Here the answer is that the large number of patients sympathectomized for Raynaud's disease make no such complaint.

(*c*) Total thyroidectomy has now been given a very good trial, and excellent results have been obtained and so quickly, that it has been suggested that some of the sensory cardiac nerves are divided in the course of the operation. I feel strongly that this operation should be confined to patients far gone in heart failure and that here it is of great value. Denerving operations do not interfere with the patient's physiology so much and are less mutilating.

(*d*) Revascularization operations are attractive in theory but are open to the following criticisms: Throughout the body it is impossible to induce any organ to take up a new blood supply when its own is intact, and after all the heart muscle is only short of blood during infarction.

After infarction no amount of revascularization will make fibrous scars of infarcts become contracting muscle again, and as fibrous tissue they will not require or acquire a new blood supply.

The operations have a high mortality. I feel that there is only one class of case where they might be justified, familial coronary thrombophilia in which all the male members succumb to coronary thrombosis early in the fifth decade of life.

Coronary thrombosis.—Surgery may be of some value here; especially valuable have I found the injection of the left upper thoracic ganglia with novocain to reduce the pain and possibly remove vasoconstriction. The heparin constant intravenous drip prevents extension of the thrombosis in the coronary vessels and absolutely stops the formation of those mural thrombi over the infarcted area which cause dangerous embolic accidents just when the patient is emerging from the cardiac wood.

Dr. H. E. Mansell: *Palliative operations.*—The surgeon aims, either directly or indirectly, at relieving the patient of pain. The direct method is to interrupt the afferent nerve paths from the heart either by actual sympathectomy or preferably by injection. Protocain can be used more freely than alcohol, and does not produce neuritis. Its effect lasts for months, and the method is of value for patients who are unsuitable for operation. The indirect method is total thyroidectomy. One certain result of this is a lowering of the basal metabolic rate, which is likely to spare the patient's heart in much the same way that medical management does. The method is indicated where angina is associated with hyperthyroidism.

Radical operations.—These are designed to deal with one or other of the two causal factors in angina, coronary spasm and coronary disease. It seems probable that thyroidectomy acts chiefly by removing the source of circulating thyroxin and thus diminishing coronary spasm. An ingenious operation has been recently described by Raney (1939), who postulated that, whereas normally the sympathetic causes coronary dilatation, in anginal patients this action is reversed and coronary constriction results. In evidence he mentions other features of angina which suggest sympathetic activity such as peripheral vasoconstriction, tachycardia, sweating, and gastric dilatation, and also the ease with which nitrites cut short an attack and adrenaline provokes one. His operation consists in dividing the preganglionic rami of the 2nd to 5th thoracic ganglia and also the sympathetic chain between the 5th and 6th ganglia, a procedure which interrupts the efferent paths while leaving the afferent untouched. He has operated on 11 patients without fatality and with complete success. At the Lambeth Cardiovascular Clinic his operation has been performed once so far, the patient being a woman with typical angina of effort, in whom the electrocardiogram was normal and an attack could be provoked by adrenaline.

None of the foregoing operations attacks coronary disease itself nor avails to prevent coronary thrombosis, a complication which proved fatal to some of Dr. Bourne's patients even after successful thyroidectomy. Surgical revascularization is essential, and although the best technique and even the ideal grafting tissue may be yet undiscovered I remain convinced that the conception is fundamentally sound and a practical possibility. Let me conclude with a few points about cardio-omentopexy. The graft is conceived as linking up with the coronary tree, so that its revascularizing effect is general, not local. Hence the ideal indication should be

specific aortitis with narrowing of the coronary orifices. I agree with Dr. Bourne that the operation is seldom indicated in cases of cardiac infarction, for the patient either improves spontaneously or is left with a large area of fibrosis in his heart which would remain unaffected by a graft. Our experience has shown that the use of aleuronat is unjustifiable owing to the risk of the pericarditis proving fatal. The approach via Larrey's angle provides an excellent view of the left ventricle for suturing the graft, and does not involve paralysis of the diaphragm. Gall-bladder disease must be excluded, and where angina is secondary to hyperpiesia the latter must be treated, and cardio-omentopexy is contra-indicated. It is also important to exclude, if possible, gross atheroma of the abdominal aorta, which is the ultimate source of the omental blood supply. Seven out of our original 15 cases of angina pectoris (Davies, Mansell and O'Shaughnessy, 1938) have died. One patient succumbed at operation, and in the case of another, post-mortem examination was refused. In four out of the remaining five patients vascular channels were found post mortem between omentum and left ventricle. In the fifth, who had shown improvement enough for him to return to work and who died suddenly, the graft was found lying free in the left pleural cavity. Aleuronat and not suture had been used at operation, and some vascular intrapericardial adhesions had formed, which may have been responsible for his temporary improvement. Finally, it is pertinent to the present discussion to mention that one of our patients, whose angina had persisted unabated by total thyroidectomy, has been almost completely relieved by cardio-omentopexy, and now can take enough thyroid to keep him free of myxœdema.

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Dr. Courtenay Evans: Dr. Geoffrey Bourne has asked me to refer to the electrocardiographic changes following anoxæmia using a 10% or 12% oxygen mixture. Following inhalations for two or three minutes I have found that the T wave changes occur in about half the patients with angina, whose resting tracing was normal. I have had satisfactory results from thyroidectomy, and one of my patients has been free from pain (previously almost unbearable) for two years; pain recurs if too much thyroid is given; $\frac{1}{3}$ gr. a day has kept him free from myxœdema. During the past six months I have been treating severe cases by alcohol injection of the sympathetic dorsal ganglia. My colleague at the Royal Chest Hospital, Mr. Ian Robin, has been very successful in carrying out this treatment—only the upper two dorsal ganglia on both sides have been injected in four cases, and so far the pain has been relieved. I have noticed an immediate severe fall of blood-pressure and collapse of the patient, sometimes with vomiting, when the ganglion is reached, but without any serious result. It is most important that the actual ganglia should be injected and the occurrence of Horner's syndrome is a good indication that the technique has been successful. This treatment necessitates only a few days' stay in hospital and is much less severe than either thyroidectomy or cardio-omentopexy.

The Chairman: I have seen many anginal patients during many years, but only one of them have I submitted to surgical treatment. As I tell all my anginal patients, this is a much maligned disease. We are impressed by those unfortunates who succumb to or are crippled by coronary infarction; we forget those very numerous patients who live to a ripe old age in spite of their angina, or die from some other disease. Some of them in fact cease to have angina; others learn so to regulate their lives as not to be worried by anginal pain. Nevertheless I agree that there is a

limited scope for surgery in the treatment of this disease. The solitary patient of whom I spoke just now is aged 65. Angina followed a coronary thrombosis in 1928. He was able to work till 1934, when angina of decubitus first appeared. In 1935 he began to have frequent attacks of acute pulmonary œdema. When seen by me in April 1936 he had been confined to bed for four months, there were frequent attacks of acute pulmonary œdema with pink sputum, and anginal pain was brought on by the least effort. Blood-pressure 190/125. Heart grossly enlarged. Bundle branch block.

Total thyroidectomy was performed by Mr. Hamilton Bailey, April 5, 1936. On May 20, 1936, walking out of doors without angina or dyspnœa.

February 17, 1940, he wrote: "I have had no severe angina since the thyroid operation. In my opinion there is no doubt of the value of thyroidectomy."

Surgery may also be considered in those cases where the patient is more or less completely incapacitated by frequent and severe anginal attacks, brought on with slight provocation, but where there is no evidence of serious coronary or myocardial disease. For instance, a man of 62 had angina of effort nine years. For four years he has averaged 20 tab. trinitrini daily. He works hard as a builder. Blood-pressure 160/90. Radiographically heart not enlarged. Electrocardiogram stationary and normal for four years, but now, after effort, coronary electrocardiographic changes appear temporarily.

In this type of case some form of sympathectomy is, I believe, justifiable.

Section of Ophthalmology

President—MALCOLM HEPBURN, F.R.C.S.

[*March* 29, 1940, *continued*]

Malignant Change in a Case of Melanosis of the Conjunctiva

By G. T. WILLOUGHBY CASHELL, M.B., B.S.Lond., F.R.C.S.Ed.

History.—A married woman aged 70, was first seen in 1926 by Mr. Dorrell when her eyes were quite healthy. The appearance of each was normal and the visual acuity was $\frac{6}{6}$ in each eye with a correction for a slight degree of myopic astigmatism. She was next seen by me in my Out-patient Department in 1934 complaining of some pain in the right eye with lacrimation for the previous four years. During this time she had noticed a slight change in the coloration of the right eye. The appearance of the eye was so striking that I made a rough drawing and Messrs. Clement Clarke painted the picture, now shown, from it (fig. 1).

FIG. 1.—The eye as seen on 19.1.34.

Family history.—The family history is of importance. The patient has no children. Her mother had a "black mole" on her cheek. She has one sister who has a large "pigmented papilloma" on the lower part of the abdominal wall and a big "brown mole" on the upper part of her left chest. She also has a brother who has a large "pigmented papilloma" in the middle of his chest.

Clinical examination.—There was extensive deposition of dark brown pigment in the conjunctiva, at the limbus and in the corneal epithelium. The conjunctival pigmentation was diffuse, chiefly to be found in the ciliary region. There were two principal patches—one between 6 o'clock and 9 o'clock, the other further from the limbus at 12 o'clock. There was a further isolated plaque in the middle of the lower fornix. At the limbus there was an incomplete pigment ring with slightly thicker portions at 12 o'clock, 3 o'clock, 6 o'clock, and 9 o'clock. The pigment deposit extended into the epithelium of the cornea in two tongue-like processes, one from the upper part and one from the lower part. Slit-lamp examination revealed fine dots of pigment in the basal layers of the corneal epithelium. The whole surface of the cornea showed a fine diffuse greyish opacity. The nerve-fibres were slightly accentuated. The vision in the eye was $\frac{6}{12}$. The fundus showed marked arteriosclerosis of the retinal vessels with a few small hæmorrhages. The left eye was healthy and showed no pigmentary change. The case was seen at regular intervals from 1934 up to 1939, during which time the pigmentary deposit increased. Periodically she had attacks of conjunctivitis and in February 1939 she complained of pain and inflammation of the eye which was found to be due to a marginal keratitis. This settled down with treatment, but there was a further relapse in May 1939, which again subsided.

FIG. 2.—The eye as seen on 24.10.39.

In July 1939 at a routine examination the eyes were quite comfortable. The pigment was still marked but there was no sign of any inflammation. The vision was $\frac{6}{9}$ in the right eye and $\frac{6}{6}$ in the left.

On October 20, 1939, she attended complaining of a lump on the right eyeball which had appeared during the last two weeks. There was a very marked change in the appearance of the eye (fig. 2) which showed considerable general congestion and a reddish, fleshy tumour situated on the limbus corneæ of the right eye at 12 o'clock. It was not obviously pigmented. Numbers of dilated conjunctival vessels ran into the upper part of the growth which was 6 mm. in width and 5 mm. in the vertical meridian. It was vascular and was attached by a wide and thick pedicle to the limbus, and overlapped the upper third of the cornea. The rest of the pigment deposit in the conjunctiva was as before except that the mass in the lower fornix had also increased in size and was of hard consistency.

The patient was admitted to hospital immediately.

Dr. Le Marquand found no sign of any other melanomata in the body, or of neurofibromatosis. The urine was normal and contained no melanin pigment. The arteries were hardened and her blood-pressure was 230/130.

Operations.—On October 26, 1939, under cocaine, I dissected the growth from the limbus and cornea and applied diathermy to the area where the growth was attached to check bleeding and any possible cell permeation. I also removed the small melanoma from the lower fornix. The two tumours were sent for section and when the report came back that they were malignant melanomata I proceeded on November 6, 1939, to exenterate the right orbit under general anæsthesia. The lids were removed, as well as the whole of the conjunctiva, the globe, and the contents of the orbit. The patient made an uninterrupted recovery and the orbital cavity healed well.

Pathological report.—The pathological examinations of the tumours and of the eyeball after enucleation were made by Dr. John Mills.

To facilitate description a plan of the anterior part of the eye concerned has been drawn (fig. 3).

In this plan the iris and ciliary body are shown, pigmentation being represented by a heavy black line. The lens has been removed.

The limbus (fig. 4).—This area is somewhat vascular and shows a moderate degree of round-cell and nævus-cell infiltration. The covering epithelium varies in thickness, shows occasional polymorphs wandering out between the superficial squamous cells and marked changes in the basal cells. The latter no longer appear as a single layer of cuboidal cells, but extend into the subjacent tissue in an irregular manner, vary greatly in size and are hyperchromatic. A few of these cells contain brown pigment granules, but pigment is more evident in the interstitial spaces of the subjacent tissue and in cells (? phagocytic) seen there. The basal layer of cells has commenced to proliferate in an active and irregular manner and to invade the subjacent tissue. No mitotic figures are to be seen. This zone grades insensibly into the

Corneal epithelium (figs. 5, 6, and 7).—Here the demarcation between epithelium and subjacent tissue becomes more sharply marked as one passes over the surface of the cornea and away from the limbus, and eventually the corneal epithelium becomes quite normal. In this passage over the cornea, vesicular spaces are noticed in the deeper layers of the epithelium adjacent to the limbus, and here there is a good deal of pigmentation which is now restricted to the epithelium. Vacuolation and pigmentation become gradually less marked and eventually disappear altogether. At one point the basal epithelial cells have formed a structure which bears a superficial resemblance to the cell nests of epithelioma. The vacuolation is particularly well marked in the region where the corneal epithelium is shown in the plan as a double line. Vascularization of the epithelium extends for a short distance over the cornea.

Biopsy Reports

Tumour from the limbus corneæ.—This tumour is composed of cells varying from round to spindle shape with large hyperchromatic nuclei, a variable amount of cytoplasm, and closely packed together with little or no intercellular substance. Mitotic figures are present and their presence, combined with marked vascularity, suggests rapid growth. There is an epithelial covering to the tumour and transition from epithelial to tumour cells is indefinite. In relation to this epithelium cell nests, identical with those described in the eye section, can be recognized. Pigmentation is very variable but nowhere is it very marked. Some of the blood-vessels are lined by a single layer of endothelium, but in the most vascular area the blood is lying free in the spaces amidst the tumour cells.

Tumour from conjunctiva.—This is much less cellular and vascular than the corneal tumour and gives the impression of much less active growth. There is much more collagen intercellular substance and pigmentation is very evident, the granules being both intracellular and intercellular.

Both are malignant melanomata, the conjunctival tumour being in a less active phase.

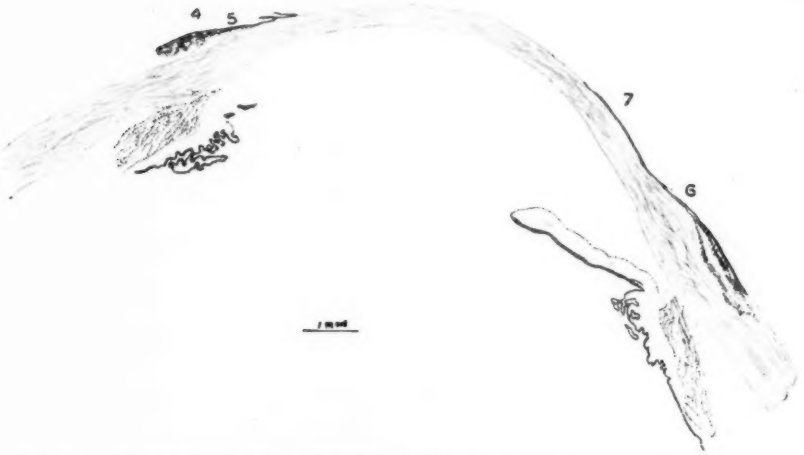

FIG. 3.—Plan of forepart of eye. The figures show the regions from which diagrams 4, 5, 6 and 7 were taken.

FIG. 4. — Limbus: 1, zone of fibroblasts; 2, blood-vessels; 3, vacuolation of epithelium.

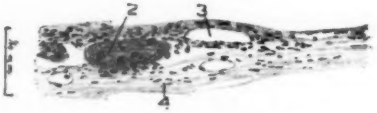

FIG. 5.—Corneal epithelium, adjacent to limbus, showing: 1, Irregularity of epithelium; 2, cell nest in relation to epithelium; 3, vascularization of epithelium; 4, proliferation of fibroblasts in subjacent connective tissue.

FIG. 6.—Corneal epithelium, further from limbus than fig. 5, showing: 1, less irregularity of epithelium; 2, vacuolation; 3, no vascularization.

FIG. 7.—Corneal epithelium from more central zone of cornea; it shows perfectly normal arrangement of epithelium and is free from pigment.

Note.—Melanin pigmentation is present in the tissues from which figs. 4, 5 and 6 are drawn, but is not shown in the diagrams.

Figs. 4, 5, 6 and 7 are all the same magnification indicated by scale on fig. 5.

Comment.—This is a case, I think, of acquired diffuse pigmentation of the conjunctiva which may be termed "precancerous melanosis", and must not be confused with congenital melanosis of the eyeball or conjunctiva.

Such pigmentation occurring in the skin is often the seat of a malignant transformation. Numerous reports can be found in the English literature of malignant growths of the conjunctiva, but diffuse pigmentation acquiring malignant characteristics seems to be a rarity.

Parsons [1] points out that pigmentation of the conjunctiva, especially at the limbus, is normal in dark-coloured races, but pigment spots in white races suggest malignant disease. He says that diffuse pigmentation is rare; when present it is confined to the epithelium. It may extend into the cornea in tongue-shaped patches towards the centre; the pigment cells at the limbus have been the starting point of malignant growths as in this case, but such tumours rarely occur elsewhere in the conjunctiva. They are highly malignant, tend to recur and form metastases, but penetration of the globe is rare. They are sometimes non-pigmented—likewise the metastases, but if pigment is present it may be intra- or extra-cellular.

Cases have been reported where a malignant melanoma seems to have arisen at the site of an acquired melanosis. Wolff and Deelman [2] reported a case in which pigmentation occurred and migrated into the cornea after removal of a tumour, and John Griffith [3] a case of a growth in the upper fornix associated with diffuse subconjunctival pigmentation. Roper [4] reported one where a brown stain in the lower half of the conjunctiva had existed for some time and gave rise to a black growth; there were also numerous pigmentary deposits in the skin. Lawford's [5] case showed a tumour arising in a pigmented patch of conjunctiva between the limbus and the semilunar fold. Rosenstein [6] suggests that sudden malignant change is found following inflammation.

Reese [7] of New York has recently reported eight cases of what he calls "precancerous melanosis". The average age at which precancerous melanosis of the conjunctiva was recognized is about 48, and the average time which elapses before malignant change ensues is about five years. The characteristics of this type of lesion are that the melanoma is diffuse, malignant areas may appear at any site—sometimes simultaneously; the areas may remain flat or are sometimes elevated. The more malignant cases arise from this type of acquired melanosis rather than from a nævus. He also reports that inflammation may frequently accompany the onset of malignant change. The treatment he suggests, once malignancy is established, is complete exenteration of the orbit, because of the extensive involvement of the conjunctiva, but irradiation may be effective in the precancerous stage.

Histologically it would appear that this type of diffuse melanoma arises in the basal layers of the epithelium and one may be justified in assuming that the tumours, according to Masson [8] are neuro-ectodermal in origin associated with the specialized sensory nerve endings. These in the conjunctiva are the tactile corpuscles of Krause and various tuft-like configurations especially at the limbus. These neural cells are thought to be capable of differentiating to form the normal chromatophores which are present in the deeper cells of the conjunctiva, especially at the limbus.

I should like to express my very grateful thanks to Dr. John Mills for his help and advice; also for the excellent drawings which he made of the histological sections.

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Binocular Loupes

By F. A. Williamson-Noble, F.R.C.S.

A few years ago, a man came into my evening clinic complaining of a sore eye. Inspection of the cornea with oblique illumination and a loupe revealed the presence of a small brown dot apparently on the cornea, so I sent him to the out-patient sister for removal of what I took to be a metallic foreign body. After a short time, sister came to tell me that she could not dislodge the foreign body. Examination with the slit lamp disclosed that the apparent foreign body was in reality a spot of old pigmented keratitic

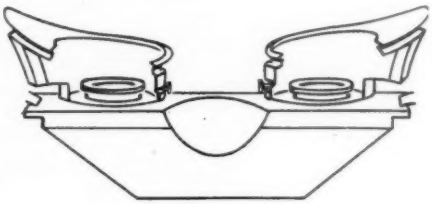

Fig. 1.

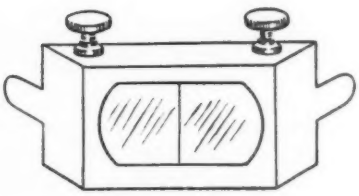

Fig. 2.

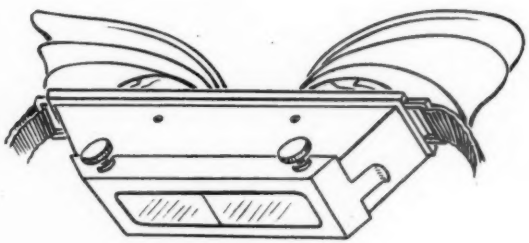

Fig. 3.

precipitates. A simple movement of the head to obtain parallax would have disclosed the position of the supposed foreign body, but it seemed so obviously what it was not, that neither of us ever thought of doing it. With the stereoscopic vision afforded by a binocular loupe its position would of course have been obvious at once.

Many other examples could be cited to show the superiority of binocular over monocular vision in examining the anterior segment of the eye, but the one I have quoted is perhaps as striking as any. Anyhow, it made me decide that two eyes were superior to one, and it is some years now since I have used the ordinary monocular loupe. The trouble with the binocular variety, however, is that the magnification is so much less. Monocular loupes are made to give magnifications of eight or ten times, but the highest power obtainable with the ordinary binocular variety is only three. In the usual pattern, the lenses are placed close to the eye (fig. 1) and it occurred to me that a higher magnification could be obtained if these lenses were further away, so I had a slip (fig. 2) made consisting of spherical lenses with an appropriate prismatic addition which could be fixed on to the outside of a binocular loupe (fig. 3). This gave a supposed magnification of four times which was a great improvement on the 3×. The instrument proved satisfactory, but it had one disadvantage: its short focal length, which meant that it had to be held very close to the patient's eye. I have always wondered if something could not be done on the lines of a telescopic binocular loupe, but was told by those who make such things that it was no use. Some time ago I saw this illustration (fig. 4) from Zeiss'

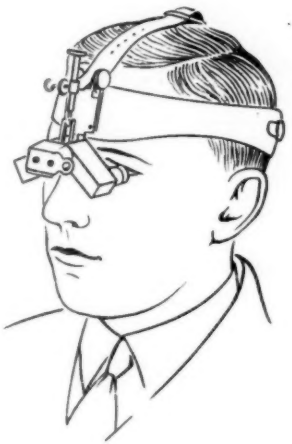

FIG. 4.

catalogue, which seemed to clinch the matter. The legend states that in spite of all this elaborate arrangement, the magnification obtained was only 5×. However it seemed something to go on, so we started with a pair of 6× binoculars in which the object glasses were placed closer together than the eye pieces. By putting a +6·50 sphere with a 12 D prism over each object glass we obtained an instrument which gave a magnification of 10× at a distance of about 22 cm. (fig. 5).

Practical experiment shows that this is an improvement over an instrument such as that with the slip attachment which gives a supposed magnification of four times at 8·5 cm. I applied one ocular of the telescopic magnifier to my right eye and one of the slip lens loupe to my left, viewed some small print placed at the appropriate focal distances through them and found that the image formed by the telescopic loupe was almost twice the height of that formed by the slip loupe. Mathematically, this can be justified. It will simplify matters if we consider linear dimensions rather than square areas. Acting on the well-known principle of the Snellen test types, it is obvious that if we view an object at say 5 cm. distance it will produce a retinal image twice as long as if it is viewed at 10 cm. A loupe therefore which produces a magnification of 10 times at a distance of 22 cm. between the observed and the observing eyes is no better than one which produces

a magnification of 5 times at 11 cm. or of 2·5 times at 5·5 cm. It seems to me that the best way of stating the magnification of an optical instrument, at any rate one used for ophthalmological purposes, would be to state its hypothetical effect at some standard distance, say 10 cm., between the observed and the observer's eyes, and one might even coin some name for the unit thus obtained—for example "magnon". On this hypothesis, a piece of plane glass would have a power of one magnon, i.e. the size of the object looked at would be unaltered. A lens system which doubled the length and breadth of an object 10 cm. from the observer's eye would have a power of 2 magnons and so on. We have found by rough experiment that the ordinary so-called 3-power binocular loupe produces a linear magnification of 1·50 at a distance of 85 mm. from the observer's eye which would be equivalent to $100/85 \times 1{\cdot}5$ at 100 mm., which is approximately 1·8. Such an instrument therefore has a power of 1·8 magnons. The loupe I showed you with the slip-on lens has a linear magnification of 2·33 times at a distance of 85 mm., which makes its power approximately 2·74 magnons, which is a distinct improvement.

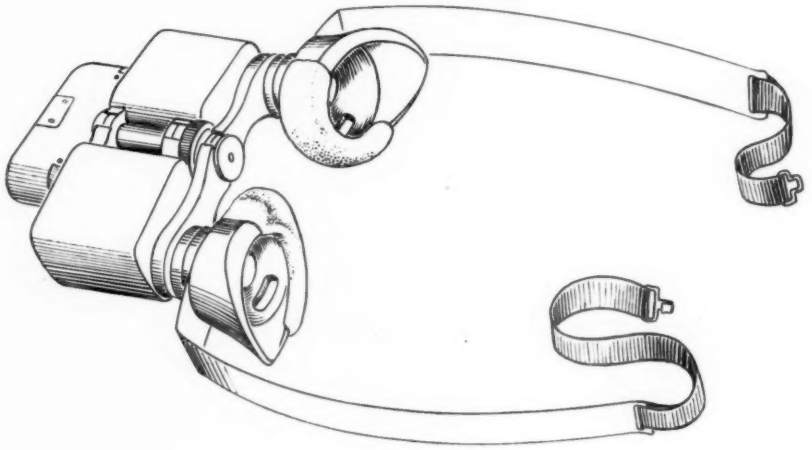

FIG. 5.

The telescopic binocular loupe has a linear magnification of 10 times at a distance of 22 cm., which is equivalent to one of 4·54 at 10 cm., i.e. its power is 4·54 magnons. The table below shows these results so that you can compare the real linear power of these instruments. If one takes the magnifications in terms of area instead of as linear functions the results of course are much more convincing because the figures obtained are 3·24, 6·76, and 20·61 respectively.

Variety of loupe	Magnification as stated by makers	Linear magnification determined by experiment	Working distance	Power in linear magnons	Power in square magnons
Ordinary binocular	3 ×	1·50	85 mm.	1·8	3·24
Binocular with slip lenses ..	4·5 ×	2·33	85 mm.	2·74	7·50
Telescopic	10 ×	10	220 mm.	4·54	20·61
Monocular	6 ×	2·33	50 mm.	4·66	21·71
Monocular	10 ×	2·7	40 mm.	6·75	45·56

It is interesting to compare these figures with those obtained with the monocular loupe. The so-called 6× variety gives a linear magnification of 2·33 at 50 mm. which is equiva-

lent to 4·66 magnons, i.e. approximately that obtained with the telescopic loupe. The 10× monocular loupe gives a linear magnification of 2·7 at 40 mm., assuming that the lens is held in close approximation to the eye of the observer. The number of magnons in this case is 6·75, which is well above that obtained even with the telescopic binocular loupe, though it is not such an effective instrument because of the absence of binocular vision and because of its short working distance.

In practice we found that the Zeiss fitting was too elaborate for ordinary work in the course of which it would probably have to be put on and taken off a score or more times a day. Eventually we tried the rigid side pieces introduced by Mr. Law and found that if these were connected by an elastic band at the back, adequate fixation was obtained provided that the vulcanite rings round the eye pieces were covered with some rubber sponge tissue.

The instrument is shown in fig. 5, and it seems to give satisfactory results. But the focus is fine and a small movement on the part of the observer or patient is enough to blur the image. With practice, however, the difficulty is easily overcome and there is some 8 in. clearance between oneself and the patient in which to manœuvre the inspection lamp. One has to be a little careful at first not to poke a finger or the lamp into the patient's eye, but this can be avoided and one can orientate oneself by looking through the holes in the lower part of the vulcanite eye pieces. This instrument can be used much more quickly than a slit lamp and corneal microscope and with the patient sitting in an ordinary chair, without a head rest: also of course it is portable. It is more comfortable for the observer to stand above the seated patient, because his head is then inclined forwards and the loupe does not exert so much pressure on the face. Its weight is certainly a drawback, but it is only worn for short periods at a time. Nowadays I use it constantly.

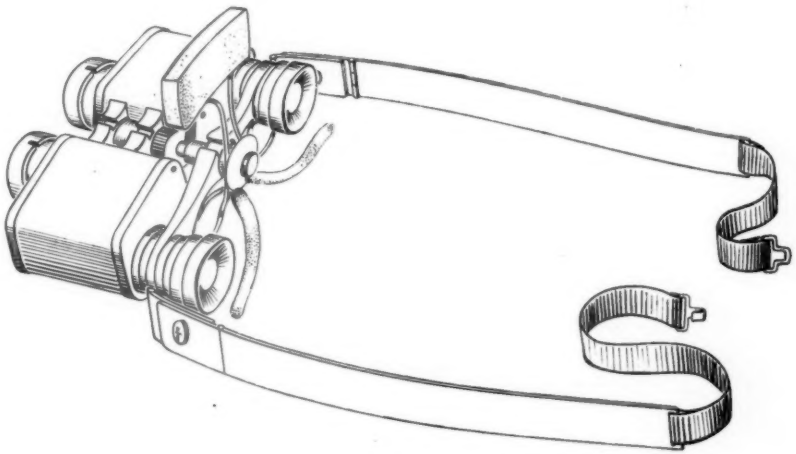

FIG. 6.

The model shown in this diagram is a later modification (fig. 6). The loupe I have been using up till now had the ordinary Zeiss type of vulcanite eye pieces covered with rubber sponge tissue. The new model arose out of a suggestion of mine that some kind of support in contact with the face lower down would be more efficient, and those who have tried this model and compared it with the earlier one will agree.

In conclusion, I should like to thank Messrs. Hamblin for the careful way in which they have carried out my ideas.

Discussion.—In reply to a question as to the price of the instrument, Mr. WILLIAMSON-NOBLE said that it was about £15. If anyone had a pair of binoculars like those which had been shown he imagined they could be converted into a loupe very cheaply.

Mr. EUGENE WOLFF asked how it differed from the telescope spectacles, to which Mr. WILLIAMSON-NOBLE replied that it had a larger magnification. The telescope spectacles gave a magnification of 1·8; the magnification with the loupe was equivalent to six times.

Asked by Mr. LAW if one of the smaller binoculars of the cheap French type could be converted, Mr. WILLIAMSON-NOBLE said that this might be done if a bigger prism were put in so as to obtain the convergence.

Section of Therapeutics and Pharmacology

President—Sir WILLIAM WILLCOX, K.C.I.E., C.B., C.M.G., M.D., F.R.C.P.Lond.

[*May* 14, 1940]

DISCUSSION ON MODERN METHODS IN THE TREATMENT OF CEREBROSPINAL FEVER

Dr. H. Stanley Banks: In 1937-38, the method of treatment used at the Park Hospital (L.C.C.) was serum (meningococcus antitoxin) in massive dosage intravenously and sulphanilamide in high initial dosage by mouth. No serum was given intrathecally since it was known that the drug appeared rapidly in the cerebrospinal fluid in amounts sufficient to cause bacteriostasis. The serum was given in dosage of 100-150 c.c. on admission, and, in severe cases, was repeated on the following day. The dosage of the drug varied from 3 grm. daily (infants) to 9 grm. daily (adults) for three days, followed by gradual reduction. The period of administration averaged eight or nine days. The following table shows the age-grouping, bacteriological classification and case fatality of *every* case admitted during the period. These included two who died within a few hours of admission, one infant admitted in the chronic stage in fifth week of the disease, and one death from intercurrent ascending pyelitis. The table, therefore, represents the *gross* fatality rate of the series. The disease was, at this period, sporadic in incidence.

TABLE I.—SERUM AND SULPHANILAMIDE, 1937–38.

Age-group	Cases	Bact. Group I	Bact. Group II	Bact. Group Inagglut.	Bact. Group Not Bact. verified	Deaths	Gross fatality rate %
0–	11	2	5	1	1	2	18
1–	10	3	3	—	—	2	20
5–	23	8	1	—	1	2	8·7
20–	21	8	3	—	5	4	19·5
40+	6	3	1	—	—	2	33·3
	71	24	13	1	7	12	16·9

The age-grouping in Table I is not dissimilar from that shown in Table II. Indeed it shows a smaller proportion in the unfavourable age-period under 5 years. Clinically, the cases were of roughly similar severity to those in the next sporadic period 1938-39 (Table II), yet the difference in the gross fatality rate was considerable. The dosage of the drug employed was similar in the two series, but, in the later series, approximately half the cases were treated with sulphapyridine. The statistical evidence, so far as it goes, shows no practical advantage gained from serum administration. I have already published some clinical evidence from the same series (Banks, 1939) that high intravenous dosage of serum does not compensate for low dosage of sulphanilamide. Accordingly, in spite of theoretical considerations, and experimental evidence (Brown, 1937; Branham and Rosenthal, 1937; Branham, 1940), I am not at present convinced that serum administration is necessary or desirable, even as an adjuvant to chemotherapy.

Table II shows the age-grouping and fatality rates of all cases received during the sporadic season 1938-39 and the epidemic period January 1 to April 30, 1940. There are no exclusions whatever, and the fatality rates are *gross*. All these cases were treated with sulphanilamide or sulphapyridine, or both drugs combined in the dosage shown in Table VI, and, with a very few exceptions (mostly fatal cases), none had serum treatment.

TABLE II.—SULPHANILAMIDE OR SULPHAPYRIDINE OR BOTH DRUGS COMBINED.

	Sporadic 1938-39		Epidemic (1940)	
Age-group	Cases	Deaths	Cases	Deaths
0–	10	1	12	6
1–	22	1	29	3
5–	24	1	35	1
20–	19	0	33	1
40+	5	2	11	1
Total ..	80	5	120	12
Gross fatality rate (no exclusions)		6·25%		10%

The age-grouping is again thoroughly representative in both series. The highest age-group fatality was 50% in infants under 1 year. This was associated with the high proportion of the "encephalitic" type met with especially in infants during the epidemic. The death-rate in the age-period over 40 years was remarkably low in the epidemic, one death only being recorded, a man of 74, who died of intercurrent hypostatic pneumonia.

The severe nature of the epidemic cases compared with the sporadic is reflected in Tables III and IV. In the epidemic, 41% were assessed as "severe", and 17% as "very severe", while no less than 46% had a petechial or purpuric rash, some being covered with hæmorrhages. Group I infections were present in 92% of 45 cases typed in the epidemic, as compared with 64% of 43 typed in the sporadic period. No less than 82% were admitted within three days of onset of meningeal symptoms in the epidemic as compared with 40% of the sporadic cases.

TABLE III.—CHEMOTHERAPY—CLINICAL DATA.

	Sporadic (1938-39)	Epidemic (1940)
Clinical grouping	%	%
Mild	12	15
Moderate	48	27
Severe	37	41
Very severe	3	17
Eruptive..	25	46
History—		
Stage of disease on admission		
1–3 days	40	82
4–6 days	44	13
7 days +..	16	5

From Table IV, it is seen that no less than 20% of the epidemic cases were not bacteriologically verified. This is a measure of the rapidity of sterilization of the cerebrospinal fluid under chemotherapy, since a considerable number of cases had treatment before admission to the hospital. On clinical grounds, there could be no reasonable doubt as to the diagnosis. The same fact is brought out in another way in Table IV, which shows that in only 1% was sterilization of the fluid delayed beyond forty-eight hours.

TABLE IV.—CHEMOTHERAPY—BACTERIOLOGY.

	Sporadic (1938-39)	Epidemic (1940)
Cases typed..	43	45
Group I	64%	92%
Group II	36%	8%
Not bact. verified	7·5%	20%
C.S.F. free from organisms—		
12–24 hours	77%	83%
24–48 hours	21%	15%
48 hours + ...	1%	1%

Complications.—These were not serious apart from two cases of deafness, one absolute and one partial. In the epidemic series of 120 cases, there were 11 cases of polyarthritis, 2 of glycosuria with moderate ketosis, not accompanied by coma ; 2 of multiple vesicles and ulcers formed in the purpuric areas throughout the skin surface ; 1 of severe myocarditis with gallop rhythm, which subsided after three days ; several cranial nerve palsies involving III, IV, VI, and VII ; and Jacksonian convulsions in 6 recovered cases as well as in many of the fatal cases. The high proportion of arthritis cases was a striking feature. Some cleared up in a few days, others, particularly those in the knee-joint, showed fluid and synovial thickening for many weeks. At onset, the fluid had varying degrees of turbidity and did not yield the meningococcus on culture. The drug effects included 3 cases of hæmaturia which cleared up rapidly when sulphanilamide was substituted for sulphapyridine ; 8 cases of drug rash and fever, which generally appeared about the eighth or ninth day of treatment, and 26 cases of persistent vomiting, all of which cleared up rapidly with change of drug from sulphapyridine to sulphanilamide. One case of granulocytopenia in a child was discovered on the day after drug treatment was stopped (ninth day). The white cell count, twenty-four hours later, reached its lowest level, 4,000 per c.mm. with 8% polymorphs. Thereafter, it rose rapidly and recovery was rapid. In this case, pentnucleotide was given twice daily from the date of discovery of the condition.

It is of interest to compare the fatality rates in this and Dr. G. E. Harries' series with those in the provisional figures for the first quarter of 1940 supplied to me by the Ministry of Health. I am indebted to Dr. Percy Stocks, who has kindly compiled these figures at short notice, and to Sir Arthur MacNalty for permission to use them. Table V shows that, subject to adjustment which will probably involve about 30 deaths, there were, in England and Wales, during the period, 4,388 cases amongst civilians with a fatality rate of 23·7% and 705 cases among non-civilians with a fatality rate of 11·3%. The total cases involved were 5,093 with 1,120 deaths, a fatality rate of 22%. The age-group fatality rates shown in the table refer to 787 cases of which reports on treatment were received by the Ministry of Health. Treatment was by chemotherapy, either alone or in combination with serum. The age-grouping shows a slightly lower proportion in the unfavourable age-periods under 1 year and over 45 years than is shown in my series, but, on the whole, it is not dissimilar. It is to be noted that the Ministry of Health's figures show a mortality of about 50% in each of the two age-periods under 1 year and over 45. These are obviously the ages of worst prognosis. It is worthy of note in passing that, while the case fatality rate for the country as a whole for the first quarter of the year has approximated to 22%, that of the two series reported to this meeting this afternoon aggregating 320 cases, does not amount to more than 10 or 11%.

TABLE V.—CEREBROSPINAL FEVER—FIRST QUARTER, 1940. (PROVISIONAL FIGURES.)

England and Wales	Cases	Deaths	Fatality rate %
Civilians	4,388	1,040	23·7
Non-civilians	705	80	11·3
	5,093	1,120	22·0
London (weekly notifications—crude)	331	101	30·5

Age-group fatality rates of 787 *cases reported to Ministry of Health : chemotherapy alone or in combination with serum treatment.*

Age			
0–	63	31	49·2
1–	49	11	22·4
2–	58	13	22·4
3–	43	14	32·6
4–	26	6	23·1
5–	130	20	15·4
15–	231	26	11·2
25–	135	25	18·5
45+	52	26	50·0
Total ..	787	172	22·0

Dosage.—The dosage recommended is shown in Table VI. The high dose shown for the initial period of two to three days has been used throughout in my cases, but the whole period of administration was latterly shortened to six to seven days instead of nine days. It is to be noted that the dose for infants and children is distinctly high as compared with adults, weight for weight, and should not be appreciably increased by "loading" doses at the beginning of treatment. These should be omitted altogether at the lower ages in each dosage age-group.

TABLE VI.—SULPHANILAMIDE OR SULPHAPYRIDINE.

Dosage by mouth.

I. *Initial period*	mild	2 days				
	moderate	2½ days				
	severe	3 days				
Age-group ..	0–	2–	5–	10–	15+
Daily dose grm.	3	4½	6	7½	9
4-hrly. dose grm.	½	¾	1	1¼	1½

II. *Middle period:* 2 days: ⅔ of dose.

III. *Final period:* 2 days: ⅓ of dose.

Duration of administration: 6 to 7 days. Total amount (adults): 36–50 grm.
Loading dose (1st and 2nd): add ¼ grm. below 5 years; add ½ grm. above 5 years.

For very acute cases, it is desirable to give the first or first and second doses by intravenous injection of the sodium solution of sulphapyridine. In an adult, 1 grm. given intravenously will generally cause an immediate rise in the blood level of the drug which will settle in about two hours to approximately 2 mgm. per 100 c.c. higher than the blood level before the injection. Intramuscular injection of the sodium solution is, I think, at present, overdone. The tendency is to employ it whenever there is troublesome vomiting produced by the drug and when administration by mouth is difficult, as in the comatose and resistive. The better remedy for the first of these conditions is to change the drug to sulphanilamide. This has proved to be very effective in all 26 of my cases in which it was indicated and carried out. For the comatose and resistive, the technique of the œsophageal tube passed via nose or mouth should be mastered by doctors and nurses who treat those cases. By this means, not only can the drug be given effectively, but also the requisite fluids which are essential if dehydration is to be avoided. Intramuscular injection of the highly alkaline sodium solution causes necrosis of muscle fibres, and sloughs and ulcers if, as not infrequently happens, some of the solution enters the subcutaneous tissue. The following case, an early one in my series, illustrates the futility of repeated intramuscular injections, when there is persistent vomiting and dehydration:—

S.B., aged 2½ years, admitted third day of disease; profuse purpuric rash; repeated coffee grounds vomiting from admission until death thirty-six hours after admission. Drug administered by repeated injections of sodium solution intramuscularly. Cerebrospinal fluid content eighteen hours after treatment commenced was 9·8 mgm.%. In spite of this high figure, the child died, with symptoms of dehydration. Vomiting was persistent to the end, and, unfortunately, parenteral salines were not given.

Causes of death.—The main cause of death in my epidemic series was an acute encephalitis. The main brunt of the onslaught was borne by the brain itself and not the meninges in a certain very acute type of case which might be called the "encephalitic type". The syndrome is one of septicæmia, multiple hæmorrhages, including profuse purpuric rash, and acute encephalitis, with no meningeal exudate. Clinically, there is profound coma and little rigidity. The duration of the illness from onset to death in five cases was fifteen to thirty hours. In two of these cases there was extensive adrenal hæmorrhage, and, in these, the pulse was imperceptible from admission. The latter syndrome has been called in America the Waterhouse-Friderichsen syndrome (Clyde and Neely, 1939). Three of the cases were infants. The following is a typical example:—

A.H., aged 5 months, admitted eight hours after onset; complete coma; large hæmorrhages—tense pulsating fontanelle, not relieved by two lumbar punctures at three hours' interval. Died fifteen hours from onset. Post mortem, meningeal and ventri-

cular exudate negligible. Brain tissue in sections showed great congestion and œdema, perivascular infiltration, widespread capillary hæmorrhages and thromboses, and extensive nerve-cell degeneration.

Somewhat less acute was the "encephalo-meningitic" type, the duration of the illness from onset to death being five to six days. Two varieties were encountered (*a*) that in which there was severe widespread acute encephalitis, and also some meningeal exudate in addition. This type was represented by a man, aged 22 years, who was completely comatose for three and a half days before he died, and who had also turbid cerebrospinal fluid, with meningococci, Group I. Post mortem, the meningeal exudate was minimal, and brain sections showed similar appearances to those described above, but with more marked perivascular infiltration, (*b*) the second variety was represented by three infants, all of whom had slight acute encephalitis, but profuse thick purulent exudate all over the *vertex* of the brain. The outstanding clinical manifestations in this type were repeated convulsions and deep coma. The other causes of death were well-recognized types: (1) Hydrocephalus from subarachnoid block in an infant admitted in the third week of the disease; (2) toxæmia with dehydration from excessive vomiting; and (3) intercurrent hypostatic pneumonia in an elderly subject.

Conclusions as to treatment.—(1) At present two drugs should be used and each has its indications.

Sulphapyridine by mouth is first choice, but, if it causes vomiting twice, nausea, depression or hæmaturia, it should not be used further, nor should the sodium solution be injected as is the present common practice. These symptoms are clear indications for the change of drug to sulphanilamide, and this change may be needed in about a quarter of the cases. As sulphanilamide is less potent than sulphapyridine, the dosage must be adequate (9 grm. daily for an adult in the initial period of two to three days and gradually reduced). There is some recent evidence, both experimental and clinical, that a third drug, sulphathiazole is about as potent against meningococci as sulphapyridine and is less liable to cause vomiting. This may yet be the drug of choice.

(2) The dosage scale recommended is designed for sulphanilamide; it is somewhat high for sulphapyridine but appears to be safe if not exceeded. The scale dosage is considerably higher for children than for adults, weight for weight. Consequently, in children, it should never be exceeded, and any increment in the first two "loading doses" should not exceed ¼ grm. No loading dose is necessary at the lower ages in each dosage age-group.

(3) The period of administration in the average case should not exceed six to seven days. Drug rash and fever, although relatively harmless, become a definite risk about the eighth or ninth day of treatment. Granulocytopenia is a rare risk, but probably depends largely upon idiosyncrasy.

(4) Intravenous sodium solution of sulphapyridine in two initial doses each of 2 grm. for an adult, diluted in three volumes of saline is recommended for *very acute cases*, and, in suitable dosage, where the drug cannot be given by mouth or catheter. The concentration of the drug in the cerebrospinal fluid some two hours after intravenous injection of 1 grm. settles to a level of about 2 mgm.% higher than that before the injection. There is, however, no need for injections in the average moderately severe or mild case.

(5) Intramuscular injection of the sodium solution causes necrosis of muscle fibres, and extensive sloughs and ulcers if there is any spilling into subcutaneous tissues. It should only be used when there is no other alternative, and then as sparingly as possible.

(6) Spinal drainage for two or three days is still required in a small proportion of cases to relieve pressure symptoms. Examples of such symptoms are: Slow pulse; slow respirations; headache; restlessness; tense fontanelle.

(7) Fluid administration especially to small children is of major importance in order to prevent or relieve dehydration. The technique of the nasal and pharyngeal tube should be mastered. In dehydration, delay in giving parenteral fluid may be fatal. The intraperitoneal route is often convenient and should be more widely used. Vomiting should be treated by change of drug.

(8) Variations in case fatality rates should now mainly depend upon (*a*) the proportion of acute cases of the encephalitic or encephalo-meningitic types in any series, (*b*) the proportion of subjects over 40 years of age with severe intercurrent disease. Case fatality rates over 15% in a mixed series should be viewed with suspicion if they cannot be explained on the above basis.

(9) Acute coma accompanied by a purpuric rash may indicate the rapidly fatal encephalitic type and should, therefore, be an indication for immediate treatment with sulphapyridine pending admission to hospital.

(10) Drug treatment acts more rapidly than serum. Although combined serum and drug treatment has theoretical and experimental sanctions, I have been unable to obtain any practical evidence of the value of serum as an adjuvant.

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Dr. G. Emrys Harries: Since the beginning of this year over two hundred cases of cerebrospinal fever have been admitted to the City Isolation Hospital, Cardiff. The following is a brief résumé of the treatment of these first two hundred cases :—

The ages ranged from 10 weeks to 70 years.

Cases	Age-group	Deaths
4	3 months or less	3
1	5 months	—
7	6-12 months	—
49	1-5 years	4
15	6-10 years	2
57	11-20 years	—
23	21-30 years	1
22	31-40 years	4
10	41-50 years	2
7	51-60 years	2
5	61-70 years	4

Males 107. Females 93.

All except 18 were civilian cases. There were 22 deaths, giving a case mortality of 11%. There was no death in the 18 non-civilian cases which had been diagnosed early. If six cases that died within six hours of admission, together with another four cases admitted moribund on the fourth day of disease or after, be excluded, the case mortality would be reduced to approximately 6%.

One case was a purely meningococcal septicæmia, cerebrospinal fluid being normal, and no changes apart from meningeal congestion found in the nervous system post mortem. A few cubic centimetres of blood taken during life, however, and hæmolysed with dilute acetic acid showed gram-negative diplococci in the centrifuged deposit. The cases generally have been more severe than in sporadic cases in previous years, and were particularly so during the height of the epidemic. In only two instances was more than one case admitted from the same household.

Petechial hæmorrhages were present in 41% of cases, herpes in 25·5%, and petechiæ and herpes present in 13·0% cases. One case with extensive vibices up to the size of a penny made a complete recovery.

93 strains of meningococci were isolated in culture from the cerebrospinal fluids. Of these, 90 belong to Group I, 2 showed no agglutination, and 1 strain showed autoagglutination, and could not be grouped. In 75 cases morphological meningococci were found in direct smears from deposits, but failed to grow on culture. Some of these patients had already had M & B 693 prior to samples of cerebrospinal fluid being taken. In 32 cases mostly following treatment with M & B 693 meningococci were not seen in stained smears of deposits, and also failed to grow on culture.

Complications.—Bronchopneumonia (was the chief cause of death in 6 cases). 38 transient albuminuria ; 4 hydrocephalus ; 3 iridocyclitis ; 4 bilateral nerve deafness ; 1 orchitis ; 3 adrenal hæmorrhages (verified post mortem) ; 10 arthritis (one prior to admission) ; 1 right transient hemiplegia ; 1 transient paresis of forearms ; 2 mental derangement persisted for two months; 38 transient strabismus.

Treatment.—Four tablets (i.e. 2 grm.) M & B 693 by mouth on admission, repeated in four hours' time, and then two tablets four-hourly for seventy-two hours. Then, provided the sugar content of the cerebrospinal fluid was approaching normality, the dosage was reduced to one tablet six-hourly for twenty-four hours, and then one tablet t.d.s. for a further three or four days. Children under 12 years received half the adult dosage, irrespective of the age of the child, as even infants appear to tolerate the drug quite well. Lumbar punctures were performed daily until the sugar content of the cerebrospinal fluid was satisfactory, and no case of meningitis was considered out of danger if the sugar had not returned. Only in a few instances were cisternal or ventricular punctures considered necessary. If the patient was comatose, the tablets were crushed and given in nasal feeds. If vomiting occurred after ingestion of M & B 693, or the patient was delirious and nasal feeding was difficult, the sodium salt of M & B 693 in equivalent doses was given by intramuscular injections. In severe cases the sodium salt of M & B 693 was given intravenously in about ½ to 1 litre of normal saline, in 5% glucose solution, by the Vacoliter drip method. It was generally unnecessary to cut down on a vein for this purpose. No serum was given intrathecally, but 30 to 60 c.c. meningococcal antitoxin were given intravenously in the normal saline in severe cases. Fluids were pushed in all cases, as to my mind dehydration can contribute materially towards the fatal issue, and three patients who ultimately recovered after being in coma for five, seven and ten days respectively had been given fluids by nasal feeds at four-hourly intervals. All patients were given glucose freely, and even in the mild purpuric cases a little sodium chloride was added to the fluid diet.

Since extensive hæmorrhages are not infrequently found in the adrenals, cortical extract was given in the fulminating cases intramuscularly, and salines, as already indicated, were given intravenously in the severe hæmorrhagic cases, as according to McCance in the Goulstonian lectures of 1936 sodium chloride is advocated in cases of adrenal damage. Three patients whose pulses were imperceptible on admission made complete recoveries when treated on these lines. In passing, I may mention that in hæmorrhagic cases where bromides were given as sedatives, sodium bromide was administered in lieu of potassium bromide.

The sulphapyridine reactions were not alarming. 16 developed sulphonamide skin eruptions ; 1 jaundice ; 6 marked cyanosis ; 2 transient hæmaturia ; 2 ulcerations.

No case developed agranulocytosis.

No person in attendance on these cases contracted the disease. No masks were worn, as the wearing of masks I believe predisposes to nasopharyngeal congestion and catarrh, which probably lowers the resistance of the mucous membranes.

In conclusion, I should like to give a word of warning regarding the giving of small doses of M & B 693 as a prophylactic in suspected cases. Small doses appear to be without effect on the meningococci, and what is more, the organisms are rendered drug-fast, and large doses administered later are then less effective.

Dr. Allison of the Ministry of Health Emergency Laboratory Service kindly arranged for the typing of the organisms, and Dr. Boissard carried out the post-mortem examinations.

Dr. W. R. Thrower, speaking in place of Dr. Whitelaw, gave an account of some of the recent work carried out on the clinical pathology of sulphonamide therapy, with particular reference to the treatment of meningitis with M & B 693. He gave a résumé of certain aspects of the problem which were of general interest and laid particular stress on the factors operating in parenteral therapy owing to the fact that sulphonamides as a class were sparingly soluble in water, which limited their use in the natural state, while the attachment of a solubilizing group often materially reduced their activity. The soluble sodium salts of some compounds, particularly M & B 693, retained their therapeutic activity and thus justified their use in clinical medicine, but the high alkalinity necessitated care in the manner of administration. While the intravenous use of M & B 693 soluble would appear to be the route of choice, considered opinion was that the complete barring of intramuscular medication might prevent acutely ill cases obtaining the benefit of a soluble preparation, were no suitable veins available or were the practitioner unwilling to undertake the procedure.

The direct effect of M & B 693 soluble upon muscle had been studied in various animals

and histological preparations made at different times after injections. The muscle fibres stained poorly, lost their striation, and became separated from one another by tissue exudate. After a time resolution of the changes occurred, but this somewhat surprising tolerance depended upon active circulation in the muscle, as also did the level of the drug in the blood. If the circulation in the muscle at the site of injection was sluggish, as was frequently the case in collapsed or severely ill patients, the position was different as the compound remained partly localized and was inadequately absorbed, and local necrosis could occur. In these cases with peripheral circulatory stasis only intravenous medication was likely to be effective.

The levels of sulphanilamide in the blood-stream and cerebrospinal fluid were commonly the same; with M & B 693, however, the position was different, as the levels in the cerebrospinal fluid were usually 60% of those in the general circulation, but at times only faint traces of the compound could be identified in the spinal fluid, despite adequate intake and good blood levels.

Post mortem it had been demonstrated that the cases which in life showed only a trace of M & B 693 in the cerebrospinal fluid had extensive choroidal derangement through inflammatory changes. The fact that these varying levels occurred with M & B 693 whereas the sulphanilamide content ran parallel with that in the blood-stream suggested that the former compound was actively secreted by the choroid. A further point was that shortly before death, when the secretory mechanism failed and pure filtration came into action, the levels in the cerebrospinal fluid and blood-stream approximated.

The optimum effective level of M & B 693 against meningococci in the cerebrospinal fluid had not yet been determined, but it was interesting to note what small traces could be active. Traces too small to be measured quantitatively would materially affect the investigation of apparently highly infected fluids, since growth of meningococci might not be obtained until after forty-eight hours' incubation, and this gave a warning against the too ready acceptance of negative culture reports on fluids withdrawn once treatment had commenced.

Dr. Mervyn Gordon pointed out that, as in 1915, the present outbreak was due to the chief epidemic strain of the meningococcus, Type I. At the height of the 1915 outbreak as many as 120 cases occurred weekly among recruits, and the mortality was 50%. This mortality continued until the late Martin Flack by clinical trial found a batch of serum that reduced the mortality in his district to 18·5% while it still remained at 50% in other districts. The potency of this serum was due to its anti-endotoxic capacity, and ultimately, with considerable difficulty, serum was prepared that reduced the death-rate in Type I cases, though not in others, to 10%.

He expressed his admiration of the recent advances by means of chemotherapy, and especially of the work of Dr. Stanley Banks who had obtained such a striking reduction in the mortality of cases due to other types as well as Type I. There was, however, at present too great a difference in the mortality rate of cases treated by experts and by others, and he quoted an instance of an outbreak in a remote village where there had been five cases and five deaths, the disease being mistaken for influenza. Special machinery was needed to diffuse this new knowledge to the profession generally, and to secure its early and successful application. This seemed to be a matter for the Ministry of Health, or the Medical Research Council.

Section of Odontology

President—S. F. St. J. Steadman, L.R.C.P., M.R.C.S., D.P.H., L.D.S.

[*January* 22, 1940]

A Critical Review of Recent Histological and Other Researches on

(*a*) Nasmyth's Membrane
(*b*) Enamel Structure and Formation
(*c*) The Entrance of Nerves into the Dentine

By A. W. Wellings, M.D.S.B'ham., L.D.S.Edin.

(a) NASMYTH'S MEMBRANE

Little work has been done recently on this part of the enamel surface except that of Pincus on its permeability. He devised an ingenious method whereby he was able to show that detached pieces of the membrane were permeable to such substances as lactic acid (in varying concentrations) cystine, sucrose and sodium chloride. The significance of these facts is not yet established, but they suggest that if it should prove that different specimens have different rates of permeability—a possible factor in the rate of dissolution of enamel may have been found.

It is interesting that experimental support is given, in part, to Pickerill's suggestion, many years ago, that the membrane acts as a dialysing membrane for the passage of calcium salts in solution in the saliva to be incorporated in the substance of the enamel and thus account for post-eruptive hardening. Calcium salts were not used in the experiments under consideration, but I have no doubt of their easy passage ; indeed it is well established that enamel is permeable to water and salts although but slowly so, and Klein and Amberson think the passage is along the organic constituent. Mineral substances and stains may enter it from the mouth or from the dentine beneath ; and we find that it is possible to penetrate the tissue to a considerable extent both from without or from within the pulp chamber. The conflicting views regarding the development and nature of the membrane need not concern us except in so far as they might affect our ideas of the pathology of some conditions, or are calculated to mislead as to the real state of affairs.

First as to the primary cuticle or pellicle. It is taught in certain schools that it is a calcified structure, very difficult to demonstrate as it is usually destroyed by acids ; Kronfeld going so far as to say that it is readily dissolved by acids and " therefore of no significance in connexion with dental caries ".

Other authors state that it is keratinous and highly resistant to acids. This is supported by the fact that those of us who have to demonstrate these things to students do so

by detaching the cuticle from the enamel surface by means of weak acids. There is an accumulation of evidence that the organic material in enamel (which includes Nasmyth's membrane) is one of the keratins which apparently differs in certain respects from that found in the horny layers of the skin and oral mucous membrane.

Gies satisfied himself that the organic residue obtained from enamel after decalcification was a protein but did not ascertain its nature. Rosebury stated that it was more closely allied to neuro-keratin than to the keratins of the body surface.

Pincus (1935) identified the protein of Nasmyth's membrane as a sclero-protein. This being the group of proteins of which keratin is a member. Later he defines enamel protein more particularly as containing tyrosin and resembling reticulin.[1] As this substance (reticulin) is said to be a possible forerunner of collagen—found in any reticular connective tissue, the statement that it is present in enamel protein obviously needs confirmation.

Whatever the nature of the protein in the cuticle of Nasmyth's membrane, and whether it is calcified or cornified, it is obviously like the protein in the body of the enamel, not soluble in weak acids, and the statement that it is so should be deleted from the textbooks.

There is similar confusion and vagueness in some of the facts concerning the secondary cuticle or cellular portion of this membrane. This remark applies particularly to the source of the cells and the manner and time of their formation into a membrane.

Gottlieb, Orban, Kronfeld, and others, state that it is derived from the squamous cells of the epithelial attachment. As this structure is dependent upon the eruption of the tooth, one concludes that this portion of the membrane is also, according to their view, dependent upon eruption, and one wonders if it is intended to suggest that its source is the surface epithelium. Kronfeld definitely states that it is formed by the oral epithelium during the eruption of the tooth.

Meyer-Churchill denies the existence of the cellular part of the membrane except under pathological conditions.

Noyes describes the secondary cuticle as lying between the primary cuticle and the epithelial attachment, thus acknowledging the independent formation of the outer part of Nasmyth's membrane. The actual attachment, however, which is formed at eruption, is the union of the cells of the secondary cuticle (the remains of the enamel epithelium) with the horny cells of the surface epithelium.

This is seen very clearly in Manley's preparations, where the epithelial attachment is sometimes torn away in cutting the sections. At times the break is between the membrane and the surface cells, but in places the union is so complete that many of the surface cells are found adhering to those of the membrane.

It is a mistake to conclude that because the epithelial attachment is formed during eruption, the secondary cuticle is also dependent upon the eruption of teeth, for I have repeatedly found it on adult unerupted teeth. It is entirely a product of enamel epithelium that only comes into relation with the horny cells of the surface epithelium at eruption.

(b) ENAMEL

The researches in relation to this tissue during recent years have been concerned chiefly with determining the presence or absence of organic matter and its disposition in the mature enamel, the nature of the protein present, the attempt to establish a lymph circulation, the rate of its deposition and changes subsequent to its deposition. It is now, thanks to the work of Bödecker, Beust, Leon Williams and others, generally acknowledged that the completely finished tissue contains a small amount of protein, although the chemical analyses differ from each other, and from that obtained by X-ray computation.

This may be partly explained by the excessive care taken to obtain the samples of

[1] Since this was written Pincus, in a later publication, states that the tyrosin reaction was due to contamination.

enamel free from contamination from the dentine and the mouth fluids, with the result that the surface tissue and that near the amelo-dentinal junction are eliminated, and as Bödecker pointed out, it is in these places that the organic material is chiefly found.

The chemical analyses of Sprawson and Bury (1928) 0·15%, Bowes and Murray (1935) 0·77% in this country, and H. C. Hodge (1938) 0·2—0·8% in America, have established that the organic material varies from 0·15% to 0·8%. The differences may possibly be individual to the samples examined, and perhaps to a small extent to the position in the enamel from which the samples were collected. It may be, as Bödecker states, that some samples contain a greater amount of enamel protein than others. I do not know of the existence of any reliable evidence that this is so, although I am quite prepared to find that it is true.

The X-ray estimate of Thewlis of 5% organic, though not agreeing with chemical analyses, may quite possibly be true of some human enamels, and speaking generally, nearer to the actual facts in most samples than the chemical analyses would lead one to expect.

Other points established by X-rays which are of great interest to the histologist are: (i) The thin strip of hypercalcified enamel on the surface; (ii) the gradual increase in calcification from the amelo-dentinal junction to the outer hypercalcified layer. Thewlis' suggestion that the rate and extent of this increase may have histological and clinical significance is worth bearing in mind.

We know from Chase's work on the enamel matrix that the process of calcification (or maturation as he calls it) of the matrix takes place in stages that can be recognized under the microscope by appropriate staining, during which the, at first, acid-insoluble matrix is converted into the acid-soluble completely calcified enamel. The process, according to Chase, should be completed in approximately three months or a condition of hypoplasia results. It would appear from Thewlis' results that the calcification is never so complete at the inner and first formed part of the tissue as at the outer layer, and one wonders if this increased hardness of the surface occurs after eruption or in any way depends upon post-eruptive conditions.

The experiments and measurements of Schour and Hoffman have been undertaken to establish the significance of the stratification lines in enamel and dentine. The ring-like concentric markings which are conspicuous where the striæ of Retzius are sectioned transversely are, it is suggested, analogous to the rhythmic stratification found throughout plant and animal life and exemplified in the annual growth rings of trees, the bands of starch grains and many seeds, the colour of butterflies' wings, in the shells of mollusca, the pigmentation of the iris and the lamellæ of the haversian canals in bone.

These authors point out that calcification and growth increment are separate processes which can be dissociated experimentally. In some species the rate of calcification and the rate of growth normally correspond as in the rodent incisor, but in others it varies with the species and the tooth, and time and level of formation.

They have established a definite calcification rhythm of 16 μ daily in both enamel and dentine, in all species throughout the animal kingdom. This is expressed in the alternate dark and light rings such as are seen in an exaggerated form in a section of enamel transversely through the crown of a human tooth; each dark and light area making up a complete "ring". In decalcified sections of dentine the rings can be brought out by appropriate staining. In the higher mammals (*Macacus rhesus* for instance), the incremental layers were found to vary in width in different parts of the tooth; in the gingival region they averaged 4 μ daily, in the cuspal portion it was as much as 12·2 μ, while towards the root end it was no more than 2·4 μ.

The variations in the rates of apposition and calcification are shown in human teeth by the width of the odontogenetic zone.

This is already well known from the work of Erdheim, Wilton and others, who have shown its increased width in rickets where calcification lags behind increment. Similarly in cases where the calcification rate is greater than that of growth, the zone becomes narrower or is absent.

In human teeth one imagines the conditions will more nearly approach those found

in monkeys than in other creatures where the measurements have been undertaken. If this is so, it is difficult to reconcile some of the accepted statements, as for instance, that human enamel prisms are built up of globules 4 μ in diameter, one of which is added every twenty-four hours, with Schour and Hoffman's findings in monkeys of a daily accretion of 12·2 μ in the cusp region. It would appear that the subject requires further elucidation.

Of the structure of enamel and its development there are still questions in dispute which recent research has done little or nothing to clear up.

Much confusion still exists as to the structure and functions of the enamel-forming cells and about such matters as the intercellular and interprismatic substances, the existence and source of the prism sheaths, the fenestrated membrane or honeycomb, the membrana preformativa, Tomes' processes and ameloblastic membranes, &c.

Some of the books mentioned contain statements such as that the interprismatic substance is "chiefly organic" and "less calcified than the prisms" and that "such organic matter as the mature enamel contains is chiefly in the interprismatic substance" which are at variance with the teachings of those who have hitherto been looked upon as the final authorities on enamel structure.

(Here followed a brief epitome of the more important views on the points mentioned, concluding with a description of Lams' paper with illustrated lantern slides made from Lams' original figures. These figures are not illustrated here owing to pressure of space.)

The Ameloblasts

There is no general agreement on the cytology and functions of the ameloblasts. It is true that enamel is coming to be regarded more and more as a secreted product, and the ameloblasts in the light of secretion cells; but there are certain appearances, which, if the interpretation put upon them is correct, can only mean that the cytoplasm of the cell is directly calcified to form the prism or rod.

The difficulties of studying the fine details of the structure of cells so delicate as the ameloblasts cannot easily be overestimated. The decalcification solutions which have to be used in all cases where calcification is in active progress, and the prolonged immersion in reagents which is necessary for efficient impregnation probably interfere with the staining reactions, and produce shrinkage and distortion, so that much of the cellular detail is not brought out. Add to these difficulties those of obtaining sufficiently thin sections and of orientating such a complicated form as the enamel organ with its frequent change of direction of the cells to coincide with the tortuous course of the prisms, and some idea of the problems with which the histologist is faced will be obtained.

The active cells are very much crowded together, and the thinnest of paraffin or celloidin sections always contain more than one layer of cells making it almost impossible to be sure that the picture in focus is not confused with some detail of a cell above or below it. It is, therefore, not surprising that so much is uncertain and contradictory in the published descriptions.

The external and internal ameloblastic membranes, which have been an important feature of enamel development in most textbooks have now been superseded by the "terminal bar apparatus" or a structure derived from the latter and called by Lams, the "superficial and basal mosaics". The existence of the lateral membranes, which, according to Fish and others form the prism sheath, is very doubtful and Lams offers an alternative explanation of the sheaths. The question of Tomes' processes is dealt with in a separate paragraph.

Granules and globules are described in the cytoplasm but it is not clear whether the former become incorporated in the latter or what becomes of them; and in some accounts the globules are regarded as calcospherites while in others it is specified that they are not.

Tomes' Processes and the "Honeycomb" or "Fenestrated Membrane"

According to recent descriptions, the ameloblasts are furnished with three sets of processes—the central or Tomes' processes, the lateral, which pass to cells on either side and the distal which communicate with the cells of the stratum intermedium.

The Tomes' processes are still much discussed, and it is uncertain whether they are actual fibrils developed in the cytoplasm of the ameloblasts, from the ends of which they pass to the forming enamel (Leon Williams, Mummery and others), or a secreted product of the cells (Lams, Orban, Meyer, Maximov, &c.), or their uncalcified centres (Tomes).

Some authorities describe protoplasmic fibrils passing along the processes from the cells in the direction of secretion (Lams) which are incorporated in the prisms in which they are described by Gustavson as lying in a spiral form like the wires in a telegraph cable.

The processes pass into the spaces or "cells" of the "honeycomb" or "fenestrated membrane" a structure about which there is some confusion. It is variously described as (i) a partially calcified layer on the surface of the forming enamel, the septa of the comb being the partially calcified outer part of the prisms, and the cells, the uncalcified Tomes' process, or prism centre (Tomes); (ii) a network of the fibrils composing Tomes' processes which here spread out fanwise and cross and intermingle to be again drawn together to form the prisms. According to this description these fibrils form the basis of both prism and interprismatic substance (Mummery); and (iii) as a region of partly calcified interprismatic material developed from the "terminal bars" in the spaces of which the uncalcified Tomes' processes and granules of pre-enamel are found, the whole area being, according to Lams, identical with Huxley's membrana preformativa.

The interprismatic substance.—The views on this differ so much that the student is left in a state of bewildered doubt as to its existence (denied by Walkhoff, Tomes ?), or if it exists whether it exerts a cementing function (denied by Meyer) and whether it is wholly inorganic in nature (as stated by Leon Williams, Hopewell-Smith, Mummery and others); or is entirely organic (v. Ebner); or partly calcified but less so than the prisms (Meyer, Orban, Mellanby, and others). Similarly its origin is equally obscure, and it is still under discussion whether it is secreted by the cells of the stratum intermedium as maintained by Leon Williams, or is calcified intercellular fluid (Hopewell-Smith); or is a product of the enamel cells—an intercellular deposit (Fish); or is derived by proliferation of the recently described "Terminal Bars".

That it has a constitution differing from the prisms is supported by recent X-ray investigations of enamel (Thewlis and others) and examination by polarized light (Keil); and these, together with the histological and histochemical evidence should be sufficient to entitle one to state quite definitely that the interprismatic substance is a distinct entity, although as yet its nature and source are still under discussion.

The prism sheath.—The possibility of staining mature enamel with silver nitrate has long been known. Underwood and Wellings showed stained edges of prisms in ground longitudinal sections of human enamel in 1913. This was independently shown by Leon Williams ten years later.

In the early accounts of enamel structure (Retzius, Swann, Owen), membranous sheaths or tubes are described "which enclosed the earthy matter of the minute prisms and served as the mould in which it was deposited". Recently rediscovered by Lams, Malleson, and Leon Williams, the sheath is still the subject of conflicting discussion, and it has not yet been definitely ascertained whether it is a distinct structure independent of the interprismatic substance (Malleson, Fish, and others), or is identical with it (Meyer, Orban); or whether it is derived from the lateral membranes of the ameloblasts (Fish), or, as stated by Lams, is developed from the "terminal bars". In this connexion it is permissible to call attention to the fibrils which are a marked feature of certain stages of all developing enamel. In very early enamel formation they take a brown coloration with the Bielschowsky process, similar to the collagenous fibrils in the pulp. It is not possible to say whether these are protoplasmic processes of the amelo-

blasts (Tomes' processes) or prism sheaths, as they appear before the definite prism structure is established.

Later on in the young uncalcified enamel, and in the mature tissue when it has been suitably embedded they stain deeply with basic dyes and have been interpreted as prism sheaths (Lams, Malleson, Leon Williams, Fish, and others, &c.). There is, of course, the possibility that they arise, not as a direct product of cellular activity, but at some stage in the process of the transformation of the colloidal secretion of the ameloblasts into the crystalloid structure of the finished tissue. This may also apply to the mysterious membrana preformativa which has been described in so many situations as to be almost ubiquitous. It is to be noted that Lams, like Huxley, identifies it with the "honeycomb" and the "fenestrated membrane".

Lams' Views on Enamel and its Development

Lams agrees with the accepted view of the prismatic structure of enamel, the prisms being formed within a sheath and united by an interprismatic cement substance. It is in his views of the origin of the latter and the formation of the sheaths and the manner of the deposition and calcification of the prisms that the chief interest of the paper lies.

It is necessary first to say a few words about "terminal bars", an expression in use in modern histological textbooks and some works on dental histology. They are associated with columnar epithelium on free surfaces. Orban describes them as thickened intercellular material which closes the intercellular spaces. Their origin is, however, still obscure. They are variously derived from intercellular bridges, thickened intercellular substance or from the protoplasm of the cells. Their function is to close the intercellular space to prevent the escape of lymph and the entrance of noxious liquids or substances. This thickened intercellular substance proliferates, and, according to Lams, produces two structures situated about the inner and outer ends of the ameloblasts, and called, the inner—"basal mosaic", and the outer—"the superficial mosaic". It will be seen that they correspond to the internal and external ameloblastic membranes, and they appear in a completely vertical section as uniform lines across the ends of the cells. It is only in oblique sections that the mosaic character appears. The internal structure is found only during calcification, but the external persists throughout the life of the cell. It is from this material that the interprismatic substance is formed, and it is stated that the calcium salts pass from the stellate reticulum, through the superficial mosaic to the ameloblasts, and through the intercellular material to the inner mosaic and on to the interprismatic material.

The proliferated terminal bar substance which is found between Tomes' processes takes the same stains as the granules in the ameloblasts and later in Tomes' processes; but presently the edges near the latter differentiate, and from this the prism sheaths are formed into which the granules of pre-enamel are deposited. It is this collection of interprismatic substance and pre-enamel within the sheaths that constitutes the honeycomb—the membrana preformativa.

The mechanism of the formation of an enamel prism and its sheath, and of the interprismatic substance, is explained in the following manner:—

The inner terminal bars, at first simple thin lines, gradually thicken and there appears a difference between the sides of the bars and the middle portion which becomes less easily stainable. It is from this part that the interprismatic substance arises. The sides of the bars which are more deeply staining, are extended to form the rod cylinders or prism sheaths as we call them. Into the cylinders thus formed the ameloblasts secrete the granules of pre-enamel which later calcify to complete the process.

The great proportion of the calcifying salts come from the colloidal substance occupying the spaces in the stellate reticulum, although Lams thinks it possible that some may come through the dentinal fibres, which he says sometimes end in the interprismatic substance, and he shows them in earlier stages between the ameloblasts and even as far as the stellate reticulum.

He states that the calcifying liquid penetrates by way of the interprismatic substance, the calcium salts, one presumes, passing through the prism sheath to the pre-enamel. Lams seems also to agree with von Ebner's statement that the salts may pass through the protoplasmic filaments of the ameloblasts to the enamel—but the text is vague on this point.

Summary of Lams' Views

(1) Enamel is formed of hexagonal or pentagonal prisms, with short interprismatic bridges passing from one prism to another.

(2) There are definite limiting membranes on the prisms, very delicate, and scarcely more stainable than the prism body which appears to be a condensation of the prism periphery.

(3) In reality the sheath is derived from the proliferation of the terminal bar substance surrounding the Tomes' processes.

(4) The prisms are joined by a cement, the interprismatic substance, also derived from the terminal bars.

(5) The ameloblasts have no cell membranes. They are connected to each other and to the cells of the stratum intermedium by intercellular bridges.

(6) They are surrounded at their outer ends by a thickened, possibly intercellular material, forming the terminal bars, which in a vertical section is shown as a distinct line resembling the external ameloblastic membrane ; but in an oblique section has a mosaic effect—the superficial mosaic. This persists, according to Lams, throughout the life of the cell.

(7) A similar structure appears at the inner ends of the cells during enamel formation. It surrounds the Tomes' processes, which are the truncated ends of the cells projecting through the mosaic towards the forming enamel.

(8) The contracted Tomes' process, midway between the mosaic and the forming enamel, expands again to the width of the prisms—and in this expanded portion protoplasmic fibrils appear arranged longitudinally in the direction of the flow of secretion.

(9) Granules, which from their staining reactions suggest the kerato-hyaline granules of the hair, are formed in the cytoplasm of the ameloblasts.

(10) The inner terminal bars thicken—there is a differentiation of the edges which are extended to form the prism sheaths—the middle portion forming the interprismatic substance.

(11) In this meshwork formed by the terminal bars, Tomes' processes are passing, and along the processes the granules of pre-enamel are secreted to collect within the cylinders which form the prism sheaths.

(12) The calcific material which is stored in the colloidal substance of the stellate reticulum passes via the intercellular spaces of the stratum intermedium, through the superficial mosaic to the ameloblasts ; and from there chiefly through the intercellular substance to the inner mosaic, and on to the interprismatic material, through which substance the calcium salts are chiefly distributed to the prisms.

(13) Some also pass through the protoplasmic filaments of the ameloblasts, and possibly some along the dentinal fibrils which may penetrate into the enamel organ.

(14) As the pre-enamel calcifies and the enamel substance grows in thickness, the rods settle against each other, become parallel and assume the prismatic form.

(15) The interprismatic substance is reduced to a minimum and as the edges of the prisms close together it is often very difficult to distinguish the cementing substance.

(16) The structure of the enamel prisms is homogeneous according to Lams.

After a study of the conflicting views on the points raised in the foregoing review, the necessity of further research becomes obvious.

With regard to the statement that the interprismatic substance contains more organic

material than the prisms, in so far as it is founded on Lams' work, I would point out that it is based entirely upon the staining reactions of Tomes' processes and the proliferated terminal bar stuff which is said to be basophilous. That, however, applies chiefly to the edges near the processes where the sheaths are developing. The portion which will form the cementing matter stains much more lightly. In the meantime granules of pre-enamel which are also basophilous and probably keratinous in nature, are being secreted by the ameloblasts and pass along the Tomes' process, crowding into the cells of the honeycomb packed into the prism sheaths which form the walls of the honeycomb cells.

I do not say that this is a correct interpretation of the process of enamel formation—indeed the question requires further investigation; but Lams' description affords no support to the assertions of Orban, Kronfeld, Noyes and others as to the organic nature of the interprismatic substance and the *almost* entirely inorganic prisms.

(c) NERVES IN DENTINE

There is an increasing accumulation of evidence from many quarters that nerve-fibres do really penetrate the dentine. They have been demonstrated within the last decade by numerous investigators.

Sealey (1932) describes nerve-fibres in the horn of the pulp which enter the dentinal canals directly, but at the sides and in the root portions of the pulp, he figures fibres running between the odontoblasts and the dentine and bending into the canals.

In addition to these intertubular fibres he shows coarser fibres winding in the matrix and giving off branches which are said to enter the tubules.

These extratubular fibres vary in thickness and are apparently in the odontogenetic zone only. Some sections taken near the surface of the crown show fibres which suggest nerves, but further work is necessary.

Tojoda (1934) published another paper with further work on this subject, using his own special technique for the Bielschowsky process. He shows nerve-fibres in the tubules which they enter directly from the pulp and a nerve-fibre running horizontally in the odontogenetic zone and giving off branches which apparently enter the dentinal tubules in the calcified dentine. He does not connect up his nerve-fibres with the general nerve distribution of the pulp, but taken together with the other evidence, it affords valuable support.

Münch (1935) describes nerve-fibres accompanying the dentinal fibrils in the tubules, and extratubular fibres that cross the dentinal canals and give off lateral branches. He has, I believe, since published another paper in which he shows nerve-endings in the enamel.

Van der Sprenkel (1936) has found looped nerve endings on the dentinal fibrils in the dentine of a human canine.

Tiegs, O. W. (1932), using Bielschowsky preparations describes fine nerve-fibres beneath and in the odontogenetic zone which terminate in minute leaf-like expansions on the dentinal fibril. Some of the nerve-fibres he has seen in the calcified dentine. Occasionally he has found coarse fibres passing into the odontogenetic zone which sometimes branch into fine filaments with end-organs applied to the dentinal fibrils. He also found end-organs on the odontoblasts.

Lewinsky and Stewart (1936). The work is well known to members of this Society to whom it was first demonstrated. Of the two types of nerve-fibres described as passing into the odontogenetic zone, I was, after a first inspection, doubtful about the coarse, extratubular fibre being nerve, but after a most careful examination of a number of sections I have come to the conclusion that they are quite definitely nerve-fibres.

Bradlaw, R. (1936 and 1939), has done much work on the nerves in and around the teeth and in his latest paper showed some terminal loops in the odontogenetic zone, and some expansions attached to the fine nerve twigs between the odontoblasts, round or pear-shaped bodies, similar to the expansions seen by Tiegs. He is unable to decide

FIG. 1.—A network of fine fibres near the surface but below the basal layer of Weil. Bielschowsky preparation. × 700.

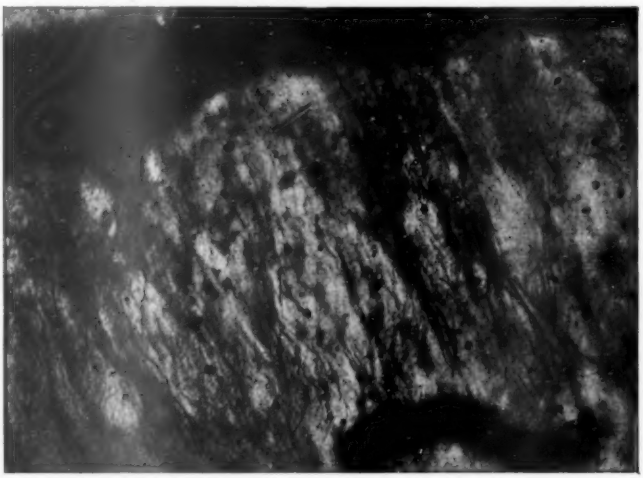

FIG. 2.—A nerve fibre which can be traced to its nerve bundle running into the dentine where it is lost in the deeply stained odonto-genetic zone. Bielschowsky preparation. × 800.

whether they should be regarded as end-organs or as nerve-cells. He has traced undoubted nerve-fibres into the dentine but is unable to decide as to their course in the dentine.

He figures a fibre entering a tubule (in cross section) from the matrix.

Bradlaw seems to doubt the nervous nature of the fibres entering the tubules, because of some experiments in severing the main nerve supply.

Speaking for myself, I find less reason to doubt the nature of these intertubular fibres than those situated outside the tubules in the matrix, for Stewart and Lewinsky's preparations trace them right back to the main nerve. Also they can be seen definitely *inside* the tubules, and if there were any likelihood of their being v. Korff's fibres, this point would settle the question, for the latter are connected with, and are a part of, the matrix (*see* fig. 3).

In the pulp, it is sometimes very difficult, if not impossible, to distinguish the two types of fibre. The conventional difference in the silver preparations is, of course, the yellowish-brown staining of the connective tissue fibres and their wavy or corkscrew character;

FIG. 3.—v. Korff fibres of pulp running into the dentine matrix. Section somewhat oblique; the spaces are the openings of the dentinal tubules. Gold chloride preparation. × 550.

whereas the axis-cylinder of the nerve-fibre is black, and has a forthright appearance that cannot be mistaken as it runs through the pulp. It is only towards their terminations that the fibres take on the looped, spiral and complex forms that have been described; and it is here that the difficulty of distinguishing them from the v. Korff fibres arises. For the latter vary extremely in thickness, and may be as fine as the finest nerve-fibre; and in their argyrophilic or precollagenous stage are said to stain black like the nerves. It is only when a fibre can be traced back to its nerve bundle that one can be sure that it is a nerve and not connective tissue.

It is this lack of means of differentiation between the two kinds of fibre that has caused the confusion, and Mummery's illustrations undoubtedly contain specimens of both, and with our present knowledge of the structure and persistence of the v. Korff fibres, it would be difficult to maintain that the fibres shown in his book as nerves are not connective tissue fibres. They probably contain examples of both. The two kinds of fibre

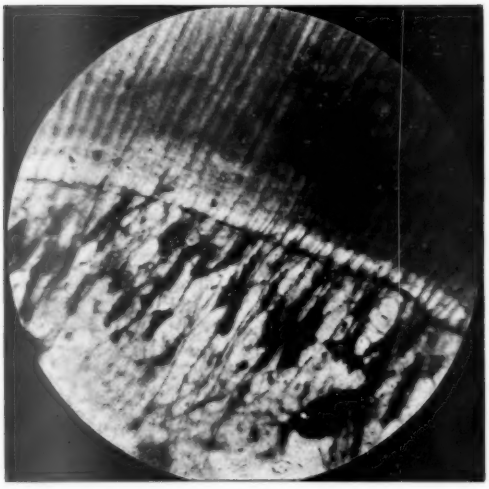

FIG. 4.—Mummery's hitherto unpublished micrograph showing undoubted nerve fibres passing from the pulp into the dentine. Probably a silver preparation. × 250.

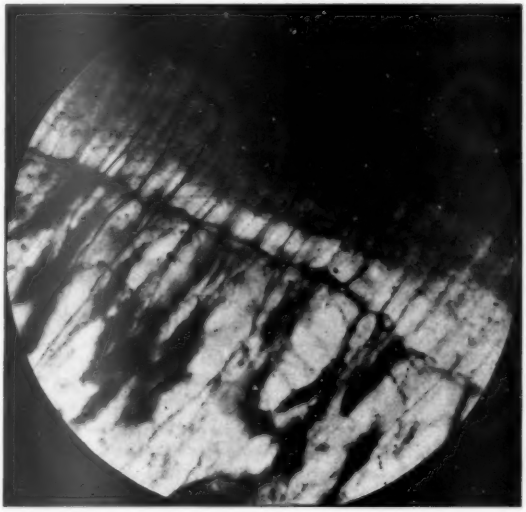

FIG. 5.—Higher magnification of the same section. Compare these fibres with that of fig. 2, which can be followed to its nerve bundle. × 800.

are clearly shown in figs. 1 and 2 (Nerves) and fig. 3 (v. Korff). I have in my possession, however, two negatives (figs. 4 and 5) which Mummery sent to me during the last week of 1924, which show fibres running from the pulp between the odontoblasts and entering the dentinal tubules, which in the light of evidence that has accumulated since that time, I have no hesitation in saying are nerve-fibres. If one is convinced that the fibres shown by Stewart and Lewinsky to enter the dentinal tubules are real nerve-fibres, then these photographs of Mummery establish his claim to have demonstrated the presence of nerves in the tubules of human dentine.

A weak point in Mummery's work was, however, his failure to show the connexion of these fibres with the main nerves, and his description of the breaking up of the axis cylinder into its constituent neurofibrils does not seem to be in accordance with the facts.

Stewart and Lewinsky have, however, supplied the missing connexion.

I cannot find out if these photographs have been published previously. It is difficult to believe that Mummery should not have reproduced them, either here or in America, for they are more convincing than anything shown in his book. Dr. Lewinsky, who has seen them, has no doubt of the character of the fibres. At the time probably Mummery thought the controversy over the fibres was at an end, and was preoccupied with the nerve-cells.

There is much uncertainty about the almost mythical plexus of Raschkow (fig. 1). It is probable that the nerve arrangement varies extremely in the pulp, and it is possible that the conflicting descriptions are due to this variation.

(Some illustrations were shown of the nerve distributions and the breaking up of a nerve bundle, and entanglements of fibres that may be called plexuses. They are from different teeth, some gold preparations, others silver. These are not illustrated owing to pressure of space.)

It is coming to be recognized that the three varieties of sensation with which the teeth are concerned, i.e. touch, temperature sensations, and pain, are mediated by different types of nerve-fibres.

Touch by large myelinated fibres, temperature by myelinated fibres of an intermediate size, and pain by small myelinated or unmyelinated fibres.

In a series of experiments on five cats and one dog, Windle found that extirpation of the pulp brought about degeneration of those cells in the gasserian ganglion which supply the fibres of the pulp nerves.

Most of the cells affected were of the medium or small-celled kind.

Pulps stained with osmic acid, pyridine-silver and chromic acid, showed many medium-sized and small myelinated fibres, the largest of which were 9—10 μ in diameter, the majority being less than 5 μ, while a few with very thin myelin sheaths were only 2 μ in diameter. There were no large myelinated fibres, and only a few fibres unmyelinated. This latter observation is not substantiated by Brashear (1936) who undertook a similar investigation. He found that unmyelinated fibres formed 22% of the total, small myelinated fibres, less than 6 μ in diameter, were 28% and medium and large fibres (6—10 μ or larger) constitute the remainder. It follows then that the great majority of the nerve-fibres in human pulps are of the medium and small myelinated or unmyelinated varieties; and that pain is therefore transmitted by these fibres.

The larger myelinated fibres which are concerned with the transmission of touch are to be found predominantly in the periodontal membrane.

The transmission of painful impulses by small myelinated fibres is not in accordance with what is known of the fibres that perform this function in the spinal nerves; but Windle points out that "there is good evidence that small myelinated nerve-fibres mediate painful impulses in other regions," and Brashear suggests that a functional type of fibre which in spinal nerves is unmyelinated, has developed in the cranial region into a myelinated fibre indicated by a thin sheath of myelin.

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Section of Dermatology

President—Major W. J. O'Donovan, R.A.M.C.

[*April* 11, 1940]

Chairman: A. M. H. Gray, C.B.E., M.D.

Connective Tissue Nævus.—Godfrey Bamber, M.D.

Mrs. A. D., aged 39. The nævi were found when the patient sought treatment for periungual tumours on the toes. She had also a florid adenoma sebaceum of the face and suffered from epilepsy. In the right wrist was a soft subcutaneous neurofibroma—two similar nodules had been removed some years previously from the same arm and this diagnosis established histologically. There was a basal-cell epithelioma in the right groin. The nævi, faintly yellowish white in colour, were found on the back and flanks (fig. 1). The mouths of the follicles were more apparent than those of the surrounding

Fig. 1.—Connective tissue nævus.

normal skin, and a few large solitary comedones were seen in the nævi near the spine. The flat surfaces of the nævi were slightly raised and both looked and felt like recent intradermal injections, an apt comparison suggested by Twiston Davies.

Histology (Dr. Freudenthal).—In the cutis are three fairly sharply defined round or oval areas, the largest of which occupies almost the whole depth of the cutis except for a narrow subepidermal zone, and raises up the otherwise unaltered epidermis over it. The collagen bundles in these areas have lost their fine fibrillary structure and seem to be swollen and fused together. Some of the bundles stain orange with Van Gieson.

Except for a few broken fibrils elastic tissue is absent (fig. 2). The cutis shows no infiltration and no inflammatory changes.

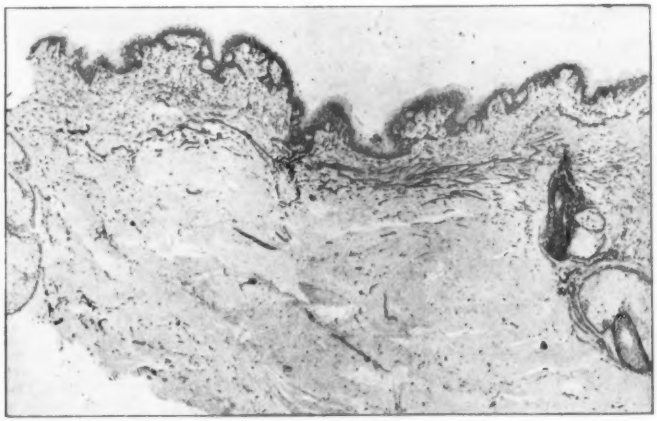

FIG. 2.—Section showing disappearance of elastic tissue.

Comment.—The connective tissue nævus is seemingly rare as only a few have been recorded. The malformation may arise from any component of the connective tissue. Gutmann distinguishes two main types, one where only the collagen is affected and the bundles become hypertrophied and homogeneous, the other where the change is in the elastic tissue which is either absent or destroyed, and this change may be confined either to the papillary and subpapillary layers or to the deeper part of the cutis.

Discussion.—Dr. F. PARKES WEBER: Dr. Bamber has stated that "The connective tissue nævus is seemingly rare". This might be so from the dermatologist's point of view, but I do not think it is so extremely rare in patients with epiloia. It is found especially in those having tuberous sclerosis of the brain, and this patient is one, as the epileptic fits make quite certain. When collections of such patients are seen in some of the asylums or clinics for defective children, this type of connective tissue nævus is not found to be so very rare.

The CHAIRMAN: Is it nearly always associated with adenoma sebaceum or does it occur independently?

Dr. PARKES WEBER: Cases of tuberous sclerosis of the brain are associated with the Pringle's or telangiectatic type of adenoma sebaceum, but cases of adenoma sebaceum of the Pringle type do not always have tuberous sclerosis, and I am not sure whether this connective tissue kind of nævus has been described in those which have not got tuberous sclerosis of the brain.

Congenital Atrophy with Reticular Pigmentation.—H. W. GORDON, M.C., M.R.C.P.

Girl, aged 12. Pigmentation was first observed on the sides of the neck six years ago, which was assumed to be sunburn. It did not, however, fade but slowly spread down the trunk.

Throughout six years the involvement of the trunk and the increasing depth of the pigmentation have been progressive. From the commencement it has been noted that white islands have been present on the sides of the neck, axillæ, and groins. The hair has always been rather thin and scanty but during the last two years it has definitely been falling out and the scalp has become rather scaly. The hands have become red and have the appearance of becoming slightly "shrivelled up".

The general health and intellectual development have been normal. Both parents, and a brother aged 8, are perfectly normal. Exposure to sunlight is said to have no effect on the pigmentation.

On examination.—The hair is abnormally thin and short, though the scalp is adequately covered. The scalp has been treated for the past year and is said to be much less scurfy than previously. It is, however, slightly atrophic and scaly and shows signs of reticular pigmentation.

The whole trunk back and front is deeply pigmented, the tint being dark brown, tending to become black in the groins, axillæ and sides of the neck. In these areas there is a well-marked reticular formation. Small islands of white skin up to a split pea in size are surrounded by fine strands of pigmentation. The hands up to the wrists are reddish and the skin is slightly wrinkled—on the wrists the veins show through abnormally clearly. The appearances are those of acrodermatitis Herxheimer.

The feet show the same changes but to a much lesser degree. Both big toe nails are thickened—in one this is said to have resulted from an injury.

The mucous membranes are normal.

Further investigation has been impossible. The patient has been on a small dose of thyroid extract for four months and it is thought that the condition of the scalp has improved and the pigmentation is no worse.

This patient belongs to a rather ill-defined group in which pigmentary disturbance of a congenital nature sometimes exists together with abnormalities of the skin appendages. The American literature, as far as I have been able to discover, contains three references to this group. The most recent is that of Becker, 1939 (*Arch. Dermat. & Syph.*, **40,** 987) when an affection of three sisters is described under the title of a familial pigmentary anomaly. All three had an identical reticular pigmentation of the sides of the neck. This had persisted since infancy and was uninfluenced by ultra-violet light. A section showed melanin in the basal portion of the epidermis. There were few chromatophores, and few melanoblasts could be identified, none being of a dendritic type. In the discussion which followed, both Cole and Engman regarded these patients as belonging to a group of which they had described examples.

Cole, 1930 (*Arch. Dermat. & Syph.*, **21,** 71), published his under the title of " Dyskeratosis Congenita with Pigmentation ". The patient was a boy of 20 who since infancy had suffered from this peculiar pigmentation of the neck and chest together with recurrent blisters on the heels and a dystrophy of the nails. The anterior two-thirds of the tongue were glazed and of a whitish appearance. His hands up to the wrists suggested acrodermatitis Herxheimer. The nails had their base fixed to the skin and were grooved.

Engman, 1935 (*J.A.M.A.*, **105,** 1252), described two brothers whose condition was similar. They had been under observation for about ten years. The earliest lesions were leucoplakia of the tongue and small ulcerations of the mucous membrane, which occurred at the age of 7 and refused to heal. The finger-nails then became atrophic and ceased to grow. Pigmentation occurred at 12 and increased until it became stationary. The jaw, neck, forearms and trunk were all affected—the reticular lacework pattern being present markedly on the neck. The hands were reddish and slightly atrophied, suggesting acrodermatitis Herxheimer. The scalp was dry and coated and the hair thin and lustreless—the eyebrows were absent.

Engman regarded the netlike pigmentation with white islands as the most fundamental characteristic of the condition—atrophy of the epithelial structures being a further feature. He described his cases under the title " Congenital Atrophy with Reticular Pigmentation ".

The present case exhibits a more widespread and more marked pigmentation than existed in the aforementioned cases.

It may be that this reticular pattern is not uncommon in pigmentary anomalies of whatever sort, but the localization here is peculiar—i.e. neck, axillæ, and groins. In addition, whole islands are scattered over the abdomen. The face is not pigmented at all but on the scalp there is a suggestion of a similar process as has occurred on the body, together with a fine atrophy.

Discussion.—Dr. PARKES WEBER: This is a form of combined ectodermal dystrophy with certain characteristic features. The first feature is the extraordinary pigmentation of the neck which one might roughly call reticulate. An interesting point is that the total amount of pigment may not be actually increased, because the pigmented areas are sprinkled with numerous whitish spots. The second feature is the condition of the scalp. The hair is atrophic and reminds one of several of the known ectodermal dystrophies of the scalp, some of them with moniliform hairs. The third feature is the condition of the finger-nails, which are obviously abnormal. The free portions

of the nail are of an opaque whiteness compared with the normal nail. The toe-nails seem not to be abnormal save for both the big toe-nails. All these things put together form a striking picture: the pigmentation of the neck, the condition of the scalp and the hair, and, lastly, the abnormality of the finger-nails and of the nails of the big toes. If all the American cases showed this particular type of pigmentation of the lower part of the neck one might group this case with them.

The CHAIRMAN: Does Dr. Parkes Weber consider the skin of the hands to be abnormal?

Dr. PARKES WEBER: There is certainly some hyperkeratosis of the hands. That would be the fourth of the features I have noticed, and in addition to that the patient has acrocyanosis of the hands.

The CHAIRMAN: There is no doubt that this is a congenital defect of an extraordinary nature. I do not agree that there is acrocyanosis in the ordinarily accepted sense. The body shows pigmentation of a sort of *café au lait* colour and the scalp is similarly affected.

Case for Diagnosis (Persistent Erythema).—C. H. WHITTLE, M.D.

C. G., a man aged 40, a smallholder.

First seen on 5.11.39, when the condition had been present for two weeks.

He presented an eruption which, starting between the shoulder-blades, had rapidly extended over the greater part of the trunk, arms and legs, but had spared the face, wrists, and lower legs. It consisted of raised, bluish-red, confluent sheets with very sharp edges, and the appearance was "geographical". At the outset he suffered from fairly severe pruritus and was depressed and short of sleep.

General condition good. No palpable splenic enlargement. Enlarged firm glands felt in both groins.

No diagnosis was made and the treatment given, general ultra-violet light and arsenic internally, was merely to relieve the irritation, which it appeared to do.

Blood-count (1.4.40): R.B.C. 5,760,000; Hb. 104%; C.I. 0·90; W.B.C. 7,200. *Differential:* Polys. 79%; lymphos. 12%; large monos. 4·5%; eosinos. 4·0%; basos. 0·5%. No abnormal forms seen.

Course.—The sheets have broken up and the affected areas have steadily diminished in size leaving pigmented skin (? from ultra-violet light and arsenic) without scarring except where he has occasionally scratched. His general health has been good and he is now comfortable. There has never been any appreciable scaling.

Comment.—The features are the persistent erythema which came out rapidly—a raised figurate bluish-red erythema, very itchy, and making the patient extremely miserable. No biopsy has been done because he has been improving ever since he was first seen. The question of mycosis fungoides was, of course, thought of, but in my view that diagnosis is unlikely. I would not in such a case expect it to clear as it is doing, apparently completely, in parts. The general condition is good. There are no enlargements, apart from the glands found originally enlarged in the groins, and a recent blood-count was normal.

This man has had both arsenic and ultra-violet light, which may account for the pigmentary changes. I think the scarring which appears on the back in one or two spots is simply from abrasions due to scratching. I can only attempt to classify this case as persistent erythema, possibly one of the erythema multiforme group.

Discussion.—Dr. G. B. DOWLING: A similar case was recently under my care: a middle-aged woman whose eruption consisted at first of isolated red infiltrated patches, which eventually became confluent and almost universal. Thorough investigations had been carried out by Drs. Macleod and Muende and by Dr. Warner at Charing Cross Hospital, and she had also been at the Hospital for Tropical Diseases before I saw her. Everything was entirely negative except for the histology of the skin. This showed a moderately dense infiltrate containing large numbers of endothelial cells; some of these were clumped like multinucleated cells. This, in conjunction with adenopathy of many of the superficial glands, led to the diagnosis of ? reticulo-endotheliosis, but histological examination of more than one gland did not reveal the changes found in lymphadenoma.

I have another closely similar case.

Dr. W. N. GOLDSMITH: I have also a case very similar to this, with these rather soft cushiony infiltrates and intense itching. The histology, in the opinion of Dr. Muende, Dr. Freudenthal and myself, was strongly in favour of mycosis fungoides.

I gave a bad prognosis and was thinking of prescribing X-ray treatment when the condition disappeared. The patient has since then suffered one or two recurrences, but these have gone away again. I do not think that that would in itself count against the diagnosis of mycosis fungoides. Even in an advanced case of mycosis fungoides the actual tumours often vanish spontaneously, even without X-ray treatment. One sees more and more cases nowadays of some temporary over-activity of the reticulo-endothelium, which cannot comfortably be put into any exact group. The other day I diagnosed quite confidently a case of lupus pernio, which showed a lumpy mauve swelling of the nose and ears; and histologically, to our intense surprise, it proved to be a purely lymphocytic infiltration. This had nearly disappeared under arsenic treatment.

The CHAIRMAN: I do not think that in a case of this kind one can exclude the possibility of mycosis fungoides.

POSTSCRIPT (24.4.40).—The biopsy shows a cellular infiltrate resembling mycosis fungoides but not diagnostic. The lesions continue to disappear.

Lichen Plano-pilaris. ? Bismuth Eruption.—A. C. ROXBURGH, M.D., and ROBERT KLABER, M.D.

F. E., male, aged 29. Post office sorter.

Both his mother and younger brother have suffered from psoriasis since childhood. For ten years the patient has suffered from an eruption confined to the scalp, backs of elbows, and fronts of legs which often clears completely for a few months in the summer only to recur in the autumn.

He was first seen at St. Bartholomew's Hospital in July 1939 when he showed parakeratotic discoid lesions which were confined to the scalp, elbows and the fronts of the legs and were regarded as psoriasis. In September the patient went to another hospital and there he was given intramuscular injections of bismuth for his psoriasis. After these injections of bismuth the psoriasis cleared up and the present eruption appeared. About two months ago the brown pigmentation which is now so marked began to appear.

Condition on examination.—Very extensive follicular hyperkeratosis and plugging distributed in a reticular manner on the trunk and limbs. In places the lesions have coalesced to form plaques and there is a striking degree of pigmentation. The trunk, limbs, penis, face and scalp are all affected. In the latter situation there is a cicatricial alopecia. There is considerable irritation. The buccal mucous membranes and, to a lesser extent, the tongue, show leukoplakic lesions suggestive of lichen planus. The nails show a mild degree of longitudinal striation. There are no papules on the backs of the fingers as in pityriasis rubra pilaris.

We saw him again in February 1940 when we thought he was a case of lichen plano-pilaris. This was apparently confirmed by the lichen planus inside the cheeks and by the cicatricial alopecia of the scalp. We only learned later that he had had injections of bismuth, and we think it at least possible that the eruption is due to bismuth because horny follicular papules are amongst the eruptions which have been described as due to bismuth injections. Bismuth eruptions, however, seem to be extremely rare.

Discussion.—Dr. LOUIS FORMAN: I have shown a case before the Section with extensive lichen planus and considerable atrophy of the scalp. Treatment with both arsenic and bismuth had been given, and just before he was shown as a case of lichen planus he had finished a course of bismuth (*Proceedings*, 1933, **26**, 997 (Sect. Derm., 51); 1934, **28**, 513 (Sect. Derm., 31)).

The CHAIRMAN: A considerable number of these cases of erythematous lichen planus follow antisyphilitic treatment. Arsenic might have been given some time previously, and bismuth right up to the time when the rash appeared, and therefore, although many of them are credited as being arsenical, I always have a strong suspicion that they are due to the bismuth and not to the arsenic. I have had at least one case following bismuth treatment alone.

I consider that this is very likely a bismuth eruption.

Angiomatosis.—ROBERT KLABER, M.D.

R. G., aged 1 year and 10 months.

A few days after birth large distended veins were noticed on the right side of the chest, right arm, and right hand. The condition has not changed appreciably since. Extensive varicose venous network is present, covering both the back and front of the

right side of the chest. Similar venous varicosities are present on the right arm and especially on the right hand and fingers. Here especially they tend to form subcutaneous tumour-like masses. The nail-beds also appear to be affected. The right upper limb does not differ obviously in size from the left. The child's mother thinks that the arm is sometimes painful. Elevation of the affected limb results in a considerable degree of emptying.

The case is shown especially to obtain views as to whether any form of treatment is necessary or desirable. The question of radiation, injections of sclerosing solutions, or subclavian ligature have all been considered, but as yet no treatment of any kind has been attempted.

Discussion.—Dr. PARKES WEBER: I would describe the case as a widely distributed vascular nævus, chiefly of the so-called "congenital varicose veins" class. Congenital varicose veins are due to an abnormal development, a dysplasia, of the veins.

Dr. BAMBER: I have treated two similar cases with radon. Both of them showed a uniform blueness which I took to indicate a capillary nævus on the venous side. After a light application of radon the skin cleared up. When I saw one of the children several years later the skin was all right and the blue patches had gone, though there were complaints of pains in the limbs. I think that beta emanations are able to penetrate sufficiently to deal with the condition.

? Granuloma Annulare, ? Lupus Vulgaris.—F. S. AIREY, M.R.C.P.

G. L. G., boy, aged 9.

Cervical adenitis commenced in September 1938 after acute tonsillitis. It was confined to the left side and the gland affected failed to subside when the throat improved. It was treated with ung. iodi denigrescens. Tonsillectomy was performed in December 1938 and the same ointment was continued, but the enlarged gland did not decrease.

In August 1939 the boy had mumps. It was bilateral and soon subsided, but this gland now became much larger, and has maintained its size to the present day. The mother says that, prior to the mumps, the boy had a severe head cold with intranasal crusting of such a degree that it attracted her attention.

In October 1939 lesions similar to those now seen began to appear on the skin. The first was on the bridge of the nose. Within six weeks it had come and gone. It took three weeks to reach its maximum, about 3 cm. diameter. A fine scar was left, and is now almost invisible.

Two other lesions soon appeared over the sternum and xiphisternum, and a similar course ensued. The duration was a matter of weeks and fine scars are left with no visible residues. About this time lesions on the arms began to appear.

He came to Leicester in February 1940, where a general practitioner made the diagnosis of lupus vulgaris. Light treatment was advised by him. The boy was taken back to his home town and there seen by the Tuberculosis Officer. He is reported to have made a thorough examination and to have come to the conclusion, independently, that the condition was lupus vulgaris. He hesitated to treat the gland surgically whilst the skin lesions persisted. During February the boy had a short course of light treatment in his home town and appeared to be improving on this. As the course terminated a papular eruption of a more generalized character made its appearance on the buttocks, thighs, face, and arms.

I saw him first on March 19, 1940, and his condition then was much the same as it is now. Tissue was removed from one of the arm patches and sections made; no tubercle bacilli were seen. The complement-fixation test for tubercle was strongly positive. Blood: R.B.C. 4,883,000; Hb. 71%; C.I. 0·73; Halometer reading 7·2 μ. The red cells were a little irregular in shape, size and staining properties but, apart from this, there was nothing abnormal. Leucos. 9,060; polys. 67%; small lymphos. 26%; large lymphos. 2%; eosinos. 2%; hyals. 3%.

The lesions now present are: An almost imperceptible scar on the bridge of the nose and others over the sternum and xiphisternum. In the left pre-auricular region is another, where a lesion came and went within two weeks. Over the right mandible is another scar, still showing residual activity. On the left arm are five lesions and on the right arm three, some of which show commencing spontaneous healing. On the face there is a lichenoid eruption, but, on the buttocks, thighs and arms this eruption is more

papular and the papules are larger and raised. There is a much enlarged gland in the left side of the neck. The boy appears to be in good health and there has been no loss in weight.

Immediately on looking at the lesions on the arms the diagnosis of granuloma annulare suggests itself. The diagnosis of lupus vulgaris had been made and I feel that this disease has to be considered. The microscopic examination indicated a tuberculoma. Typical giant cells, epithelioid and small round cells were seen in the deeper corium.

At one time I considered the diagnosis of multiple patches of lupus vulgaris, with "lichen" scrofulosorum in addition, to be a definite possibility. But, on inquiring into the history, I found that the lesions appeared and went with a rapidity unusual in lupus vulgaris, and there was clear evidence not only of a tendency to spontaneous healing but several places are clearly seen where the lesions have disappeared and left only a fine scar. In my experience this does not occur in lupus vulgaris. It seems likely that the multiple lesions are those of granuloma annulare multiplex.

What of the papular eruption? It may be "lichen" scrofulosorum, for the lesions on the face are lichenoid whilst those on the hips and arms are more characteristic of a tuberculide. Yet the eruption is not very extensive. It came much later than the other lesions and appears to have remained stationary for two months. If this eruption were granuloma annulare one would expect, by now, to see enlargement of some of the papules to form lesions more characteristic of this condition. It may be that there are here two manifestations of cutaneous tuberculosis present at the same time.

Was there an initial, tuberculous nasal lesion in this case? I can find no evidence in the nose now to indicate this, but the history is suspicious.

Finally, I would like to ask: "What treatment is to be adopted?" Spontaneous cure seems possible. In proposing general carbon-arc light baths as the only measure I wonder if good or harm will result, especially as the second eruption came immediately after a course of light treatment.

Discussion.—Dr. F. JACOBSON: I quite agree that this is not lupus vulgaris. Lupus vulgaris is a clearly defined entity and if it heals the scar is depigmented, atrophic or hypertrophic. The comparison with granuloma annulare is a very good one, but one must not stick to the old classification and labelling of the different manifestations of cutaneous tuberculosis. There is no doubt that this boy is suffering from a tuberculosis and it will be interesting to see how he reacts to tuberculin. I think this is a case which shows different forms of allergization towards tuberculous infection, probably of bovine origin, and that the three different types all belong to the large group which might be classified as tuberculides. Probably this case will show a "positive anergy" illustrating the benign nature of the infection and its cutaneous response. Any kind of treatment which may possibly give rise to acute dissemination should not be tried, but apart from carefully dosed general light treatment one may perhaps try iodine in milk.

The CHAIRMAN: I showed a very similar case in May 1923.[1] This was a child who was in the care of Sir Frederic Still at Great Ormond Street. Most of the lesions were of the acneform variety, but on the forearms there were similar lesions to those shown in Dr. Airey's case, though not so sharply cut nor so rapid in their appearance. The lesions there, if examined very carefully, consisted actually of numbers of minute follicular lesions which gradually spread out in disc form; but it was classified as a case of acne scrofulosorum. As to the present case the first thing to be done is to deal with the primary focus. The child seems to have a suppurating gland in the neck, and as long as that is present there is not much chance of clearing up the condition. The result of doing so, however, may be to increase temporarily the eruption, which later should subside. Many cases of tuberculides in children follow a stirring up of some focus, either in joint or gland.

Dr. AIREY: The surgeons are reluctant to tackle the primary focus.

The CHAIRMAN: When there is such an obvious thing it seems desirable to get rid of it.

POSTSCRIPT (1.7.40).—Since the case was shown the gland has been excised and general light baths have been given. All the large lesions have disappeared and no new ones have occurred. The other, papular, eruption remains about the same.—F. S. A.

[1] *Proc. Roy. Soc. Med.*, 1923, **16**, (Sect. Derm., 101).

[*May* 15, 1940]

The President, Major W. J. O'Donovan, R.A.M.C., in the Chair.

? Reticulo-endotheliosis.—E. W. Prosser-Thomas, M.D.

H. P., male, aged 28, electrician. The eruption first appeared on the abdomen about ten months ago. It slowly extended centrifugally over the trunk, arms, and legs. The hands, feet, head and upper portion of neck have never been involved. There has been no disturbance in general health.

On examination.—There is a profuse eruption on the trunk and limbs. The lesions are yellowish-pink or ruby wine-colour macules and are scaly. Some of them are infiltrated and one or two appear umbilicated with apparent central atrophy, which may have been produced by scratching, as the eruption irritated in its early stages. There is very little irritation now. There is slight but definite generalized enlargement of superficial lymph glands. The spleen is not palpable. The patient is a sweaty and nervous man. No other abnormal physical signs were found on general examination. The blood Wassermann (19.4.40) was negative and a complete blood-count (1.5.40) was within normal limits. A biopsy has been done but the section is not yet ready.

Discussion.—Dr. F. Parkes Weber: I think the case is a very unusual one of urticaria pigmentosa in an adult. One can obtain urticaria factitia between the lesions, and the lesions themselves urticate to some extent on rubbing. The enlargement of the glands, in my opinion, is secondary to the skin involvement. The biopsy, if it shows a considerable amount of mast cells in the lesions, will confirm my diagnosis.

About 1892, Dyce Duckworth asked me to go to the Dermatological Society of London to show a case for him. The case was very like this, and the diagnosis, as far as I can remember, was urticaria pigmentosa in an adult.

Dr. W. N. Goldsmith: Has Dr. Parkes Weber, in other cases of urticaria pigmentosa in adults, seen atrophic spots? In this case, many of the lesions appear scarred. This

may be the result of secondary infection, but is perhaps more suggestive of a granuloma. Secondly, has he in other cases seen urticaria factitia in parts of the skin other than the lesions themselves?

The PRESIDENT: Dr. Parkes Weber stressed the existence of factitious urticaria, and both Dr. Goldsmith and I would be interested to hear whether he necessarily expects to see that in an adult case of urticaria pigmentosa. Another puzzling point is that the enlargement of the gland is "secondary" to the skin involvement. The pathological process whereby that is brought about is a little mysterious, for the skin is not septic and did not seem to be infiltrated.

Dr. PARKES WEBER: I think that the glandular enlargement is secondary to active cutaneous lesions. Some of the lesions in this case are infiltrated and "active". It is probable that others have been infiltrated at one time or another, although just at this moment it is only some of the lesions which are decidedly infiltrated.

In regard to the other question I take it that urticaria factitia is not always present in cases of urticaria pigmentosa. If there is no activity of the lesions I think that urticaria factitia may be absent.

Dr. A. M. H. GRAY: I agree with the President's suggestion that these glands are not secondary to the skin lesions. Here is something more than a mere skin condition; we are dealing with some reticulo-endotheliosis. The question needs investigating from that point of view. It is just possible that this man may prove to be an extremely unusual case of sarcoidosis, or possibly one of lymphadenoma or leukæmia.

POSTSCRIPT (10.7.40).—Two biopsies have been made but the histological findings are inconclusive. There is an infiltrate in the upper portion of the corium and a number of mast cells are present, but the appearance is not considered to be that of urticaria pigmentosa. There is no radiological evidence of diseased glands in the chest.—E. W. P. T.

Civatte's Disease.—E. W. PROSSER THOMAS, M.D.

Mrs. F. H., aged 52. First noticed a freckle-like staining of the sides of the face in June 1938 which she ascribed to exposure to the sun. The pigmentation gradually extended downwards over the neck and upper part of the chest and across the chin and the forehead. The central portion of the face has never been affected. The pigmented areas have never irritated. Apart from menopausal symptoms there has been no disturbance in general health.

She was first seen in February 1939, when a reticular dark-brown pigmentation was present symmetrically distributed over the areas mentioned. The buccal mucosa was unaffected and no abnormal pigmentation was found on any other part of the body.

The affected areas were treated with applications of thorium X (alcoholic solution, 1,500 electrostatic units per c.c.) at monthly intervals until October 1939. From then until about a week ago she was unable to attend hospital.

The pigmentation is now more or less confined to the neck and upper portion of the chest. Some atrophy appears to be present on the right side of the neck, but the other areas previously involved (forehead, sides of face, and chin) seem to have returned to their natural consistency and colour.

Erythroderma with Deep Pigmentation.—G. B. DOWLING, M.D.

J. M., aged 63, has been under my care for years. He lived on the Gold Coast for twenty-three years, and while there he suffered a good deal from malaria, but there have been no relapses during the past six or seven years. The present condition began nine years ago with redness and desquamation of practically universal distribution. There has been moderate irritation throughout, but little or no evidence of scratching. The whole rash has become slowly more and more deeply pigmented. The buccal mucous membrane is also pigmented. The general health seems to have been little affected. A striking adenopathy has also developed slowly. The spleen has never been palpable, and there is no X-ray evidence of enlarged glands in the chest.

Investigations at St. Thomas's Hospital revealed nothing very definite. A gland excised for biopsy was found to be fibrotic and to show a considerable degree of eosinophilia. The epidermis was deeply pigmented, especially the basal cells, and an infiltrate of a chronic inflammatory type was present in the most superficial part of the dermis. The gland gave a positive biological test for Hodgkin's disease (Gordon's test); and the blood-count, done on two occasions, showed eosinophilia 10 to 12%, but no other cells in abnormal quantities.

Dr. King, who carried out Gordon's test, believed that the test was probably positive on account of the large number of eosinophils in the tissue.

Leukæmia is excluded by the blood-count, and Hodgkin's disease seems also to be excluded.

Discussion.—Dr. PARKES WEBER: Lately there has been a tendency, as Dr. Dowling has said, to regard a positive Gordon's biological test as due to the eosinophilia of the blood and lesions in Hodgkin's disease—in fact, to regard Gordon's test as one not for Hodgkin's disease, but for eosinophilia. I think that the skin condition here is the primary one, and the glandular enlargement secondary, and that the diagnosis is not one of Hodgkin's disease.

Dr. ELIZABETH HUNT: At the last meeting I showed a woman of 64 whose condition looked very similar to the case under discussion. In both cases the pigmentation is absent on the forearms and hands, and in my case on the lower legs also. The cases differ in that the man has pigmentation of the nipples and of the mucous membrane of the mouth and my patient is unaffected at these sites. My patient has no eosinophilia. Her white count was 9,000, some 40% leucocytes, and over 50% lymphocytes. The blood urea was low, 16 mgm. per 100 c.c. The uric acid was also low. No lymphatic glandular enlargement was found, but there is a slightly enlarged liver. Stroking the skin in both these cases produces a very marked white line for a prolonged period. My case has complained of persistent irritation and loss of sleep, but looks healthy and well nourished. A more recent complaint is of muscular pain in the muscles of the thighs, and stiffness on first getting out of bed.

The PRESIDENT: There is no question of the patient having had salvarsan?

Dr. DOWLING: I do not think he has ever had arsenic. The X-ray of the chest is normal.

The PRESIDENT: I hope that if there are later observations of this man—and he appears to be of the type which might go the round of the hospitals—we shall have reports on his progress.

Section of Urology

President—JOHN EVERIDGE, O.B.E., F.R.C.S.

[*March* 28, 1940]

A Case of Megalo-ureter

By J. A. CURRIE, M.S.

E. P., aged 65 years, a married man with two children, described himself as having always been healthy, except for some difficulty, noted since childhood, in emptying his bladder completely. Four years ago, he suffered from frequency, dysuria, and one attack of severe hæmaturia. He went to the out-patient department of a London hospital, where he was investigated clinically, cystoscopically, and radiographically, but was not submitted to intravenous pyelography. He was told that he had cystitis and was given medical treatment. He attended at this clinic for three or four weeks and improved for a while, but subsequently relapsed.

Two years ago he had another less severe attack of hæmaturia. There has been none since.

He came up in January 1940 to St. Peter's Hospital, complaining of dribbling incontinence and nocturnal bed-wetting.

On examination, the bladder was found to be over-distended, with its fundus palpable at the umbilicus. There was no pain. His tongue was clean and moist. On rectal examination, the prostate was felt to be enlarged, globular, elastic and movable.

A No. 20 French gum-elastic catheter was passed with ease, and 15 oz. of purulent urine were withdrawn, which gave, on culture, a profuse growth of *Bacillus coli*.

There was no other abnormality, except a soft bluish tumour, about the size of a hazelnut, in front of the upper end of the right tibia.

He was admitted to Colindale Hospital on January 13, a catheter was tied in for decompression of the bladder, and by the 15th his bladder was empty and the catheter was draining freely. His blood urea was 50 mgm./100 c.c., and the urea clearance test was 80% of normal.

Thinking that his symptoms were due to prostatic obstruction, I decided to perform suprapubic cystostomy as a preliminary to prostatectomy, but did not feel satisfied about the association of a painless distended bladder with such purulent urine and relatively good renal function, so decided to cystoscope him first.

There was no sign of abnormality of the central nervous system.

Cystoscopy showed two large motionless holes in the position of the ureteric orifices and the possibility of megalo-ureter was at once considered, though the possibility of diverticula was not ruled out.

The bladder wall was smooth, with no trabeculation. Anteriorly, the prostatic lobes seemed to be large and formed a well-marked V, but posteriorly the internal meatus was widely open.

The bluish tumour over the tibia was excised. The clinical facts and operative findings corresponded exactly with those of the glomangiomata described by P. Masson (1924) and by Lendrum and Mackey (1939). Microscopic section confirmed the diagnosis of glomangioma, and in this respect the patient was completely relieved of his symptoms.

On 18.1.40, cystography revealed well-marked bilateral hydronephrosis and hydroureter. The ureters were about 1 in. across in their greatest diameter, and were elongated and tortuous, with a double kink. Suprapubic cystostomy was performed on 24.1.40 (*see* fig. page 588).

The patient's recovery was uneventful and he was discharged with a permanent suprapubic tube and is now attending the Out-patient Department at St. Peter's Hospital.

It was felt that in this case the grossly distended bladder demanded cystostomy. Presacral neurectomy was not thought likely to succeed in reducing the size of the ureters, which had been dilated for so many years and were probably affected by secondary inflammatory changes.

The incidence of megalo-ureter, without demonstrable organic obstruction, is extremely low, at any rate in adults. I believe that it is considerably higher in children.

During my year's residence at St. Peter's Hospital, I saw no example of the condition, but I saw a typical case in Capetown some years ago in a coloured woman of 40.

In 8,365 patients who have been investigated and treated at St. Peter's Hospital in the five-year period since January 1935, only two cases of megalo-ureter which seemed to be genuinely congenital and non-obstructive were found. These were both adult females, and both had been submitted to presacral neurectomy. In neither of these was the size of the ureter materially affected by the operation.

E. P. on 18.1.40.

The first case had suffered from incontinence for three years before admission. Four months after presacral neurectomy the ureters were still enormously dilated.

The second case had had hæmaturia and pyuria for many years and her urine was pus-laden and infected with *B. coli*. She had huge bilateral hydro-ureters, her ureteric orifices were greatly dilated, and her residual urine before operation was 50 oz. Three years after presacral neurectomy her residual urine was reduced to 6 oz., but on a subsequent occasion it was found to be 22 oz. The dilation of the ureters does not seem to have been affected.

Of five other cases considered but not held to satisfy the necessary criteria, one was excluded because he had had a stricture, for which instrumentation and cystostomy had been performed before he came to the hospital in 1926. As his urethra admitted a 20 French catheter and the cystoscopy appears to have been easy, one wonders if the stricture could have been responsible for his megalo-ureters. He should probably have been included in my list.

The other four were :— a man who had a successful nephro-ureterectomy for double ureter with pyonephrosis, a boy with advanced bilateral hydronephrosis and hydro-ureter treated by cystostomy and the retrograde passage of bougies, a man with spina bifida occulta and a dilated lower left ureter but normal ureteric orifices, and a man whose unilateral megalo-ureter was evidently due to infection.

My impression is that megalo-ureter without obstruction is much commoner in children.

Meredith Campbell (1937) found 138 cases of dilatation of the urinary passages, with no evident obstruction, in 12,080 autopsies upon children, an incidence of 1:88. He remarks that in only four of these cases was there congenital dilatation of the ureters without similar neuromuscular involvement of the bladder.

Poynton and Sheldon (1927), in a study of autopsies upon three children and the clinical histories of five others, drew attention to the ease with which valves in the posterior urethra can be overlooked, and held that while the existence of the non-obstructive type must be admitted, in most some form of obstruction could be demonstrated.

Addison (1929, 1934) refers to urethral valves in boys and to a few cases of urethral diaphragms in girls, while Meredith Campbell (1931) describes bilateral megalo-ureter, in children, due to stricture at the uretero-vesical junction.

The Museum at Great Ormond Street contains a beautiful collection of megalo-ureters, but cases in which there is no obstruction are few, and I actually saw only one specimen like my case. Another specimen was described in the notes in the Museum index, but had been packed away owing to the war. In the specimen which I saw the ureters were dilated to the size of small intestines. It was interesting to note that on cystoscopy the ureteric orifices did not appear abnormal, whereas in a female child who had a nephrectomy in 1933 for double hydronephrotic left kidney, the notes state that the bladder was atonic and the ureteric orifices gaping and motionless. In this latter case one feels some doubt as to the ultimate fate of the kidney on the normal side.

Many of these specimens and case records demonstrate the association of megalo-ureter with other congenital abnormalities, some of them extra-urinary, and the occasional association of megalo-ureter with Hirschsprung's disease has been commented upon.

Before considering presacral neurectomy, it is worth while to bear in mind the part that infection can undoubtedly play in the production of a dilated ureter. Von Lichtenberg (1926), basing his views on the experimental work of Primbs (1913), believes that acute infections producing ureteritis may result in ureteral dilatation and stasis. Braasch (1927) mentions the reflux up the ureter of cystographic media in chronic pyogenic and tuberculous infections.

This production of atonia by infection is a factor which increases the difficulty of assessing a case on whom it is proposed to perform presacral neurectomy. Nearly all of the congenital cases have some degree, usually considerable, of infection and it is not easy to determine whether the infection is a complication or a cause of the ureterectasis.

If one can exclude infection and obstruction as causes of the dilatation in a particular case, one is reduced to the non-committal expression "idiopathic", for not all the congenital cases are non-obstructive. It is to this group that the case described belongs.

According to Meredith Campbell, Israel (1901) was the first to describe this type as a separate entity. Bradford (1901), however, in an article on uræmia in Gibson's "Medicine", describes in a few lines the congenital megalo-ureter in children, most of whom suffered from incontinence. These cases are described as having no obstruction in the urinary tract.

Papin and Legueu (1904) are quoted by Campbell as first clearly describing two characteristics of these idiopathic cases. These are the large, patulous and immobile ureteric orifices and the free vesico-ureteric reflux of cystographic media. Without these, according to these authors, the case should not be called primary or congenital, though these large immobile openings may in some cases be due to infection or obstruction.

The hypotheses which attempt to account for non-obstructive megalo-ureter attribute it to an error in mesenchymal development or to some failure in neuromuscular co-ordination.

Meredith Campbell, dealing with the view that a dysplasia of the musculature is responsible, points out that the ureteral bud in the fœtus is normally wide up to the fourth or fifth month of intra-uterine life, and has no muscular investment at first. Soon after the second month muscle fibres appear at the vesical end, and between the middle and end of the fifth month envelop the entire ureter and pelvis.

Gruber (1927) in Schwalbe's work, reviews the whole subject at length. The numerous

illustrations include an excellent one, borrowed from Israel, in which the bilateral megalo-ureters of a boy of 12 are well shown. It is of interest to note that in this illustration the ureteric orifices are clearly shown as of normal size. Gruber says the condition may exist undetected for years and then suddenly make its presence felt. The association with Hirschsprung's disease is noted and it is recognized that recent views tend to attribute the atony to defects in the rhythm of ureteric peristalsis due to nervous dysfunction.

Ward (1933) reported a case in which the evidence seems to point clearly to an error in the sympathetic control of the ureteral musculature. In this patient, a man of 41, urinary symptoms had only been present for a few months. Renal pelves, calices and both ureters were grossly dilated. The ureteric orifices were normal and there was no vesico-ureteric reflux. In this respect, therefore, the criteria laid down by Legueu and Papin were not satisfied. Presacral neurectomy was performed and pyelograms made subsequently revealed a remarkable diminution in the dilatation. The ureters were capable of peristalsis, were of nearly normal calibre, the renal pelves were no longer dilated and only slight clubbing of the secondary calices remained. This improvement was maintained eleven months after the operation, as a second post-operative pyelogram revealed. This case had suffered from an acute urinary infection before operation, but the results of neurectomy were too dramatic and immediate for the improvement to have been due to subsidence of the infection alone.

The effect of presacral neurectomy in reducing the amount of residual urine is explicable in the light of our knowledge of the functions of this nerve.

Learmonth (1931) has shown that where the function of the hypogastric nerves preponderates over that of the pelvic nerves, presacral neurectomy can improve the expulsive power of the bladder, provided that the pelvic nerves are not completely destroyed and that the external sphincter is still competent. If the latter proviso is not fulfilled there will, of course, be incontinence.

It is more difficult to explain the effects on a dilated ureter.

These effects must be admitted. Whether one can be certain in advance of securing them is another matter.

I am indebted to Mr. J. A. Andrews for permission to report this case. I also desire to thank the staff of St. Peter's Hospital for permission to use the records, the Pathology Department at Great Ormond Street for access to their museum specimens, and Mr. Barrington for his help and advice.

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Discussion.

Mr. H. P. Winsbury-White: *Three cases associated with vesical residual urine.*

Case 1.—L. A., female, aged 6 years.

Complaint.—Recent attacks of fever and pain in joints; enuresis for six years.

Urine: *B. coli*; few pus cells; trace of albumin.

Excretion urograms: Mild degree of dilatation of both ureters and good function of both kidneys.

Residual urine: On several occasions amounts varying from ½ to 2 oz. were found.

Treatment.—Intermittent dilatation of bladder neck at increasing intervals over a period of four years.

Result.—Attacks of fever and enuresis ceased and residual urine disappeared.

Case 2.—H. S., male, aged 40.

Complaint.—A recent period of evening pyrexia and cloudy urine which had kept him in bed for several weeks.

Urine: Turbid with pus and contained *B. coli.*

Excretion urograms: Left side, no sign of renal function; right side, poor renal function, but no dilatation of kidney or ureter.

Instrumental pyelograms: left side: Ureter dilated to diameter of 1 in. and looped; kidney slightly dilated.

Residual urine in bladder—14 oz.

Treatment.—Transurethral resection of bladder neck, after period of suprapubic drainage.

Result.—Residual urine reduced to 3½ oz.; no further attacks of fever; degree of infection of urine reduced; striking improvement in general health.

Case 3.—F. C., male, aged 50.

Complaint.—Attacks of fever with rigors and pyuria at intervals for several years.

History.—Gonorrhœa at age of 20; treated for urethral stricture in past.

A cystogram taken two years before showed a regurgitation of opaque medium up the right ureter, the pelvic extramural portion of which was dilated to diameter of ¾ in. Investigation and treatment of his urinary tract by 15 urologists and other surgeons in past six years, without benefit.

On examination.—Urine clear, a few flakes of debris, a few pus cells and *B. coli*; residual urine, 7 oz. 26F metal bougie passed easily but stricture noted in bulb. A further cystogram showed same condition as present two years previously.

Treatment.—As a result of five days' indwelling catheter drainage, residual urine reduced to 1 oz. and improvement in general health.

Comment.—Fibrous obstruction of bladder neck often accompanies urethral stricture, and maintains residual urine in the bladder long after stricture is fully dilated.

The megalo-ureter is undoubtedly secondary to the bladder neck change.

A case of megalo-ureter associated with an infection originating in the internal genitals.

Case 4.—S.N., male, aged 20.

Complaint.—Frequency and dysuria for two years.

Urine: A small amount of pus and *B. coli.* No tubercle bacilli (guinea-pig).

Urogram: Mild dilatation of both pelves and ureters, bladder contracted.

Rectal examination: Both seminal vesicles and prostate thickened.

Two cases of so-called idiopathic megalo-ureter.

Case 5.—C. S., male, aged 25.

Complaint.—Attacks of bilateral renal colic, the passage of gravel and blood.

The urograms showed a moderate degree of dilatation of both ureters, particularly the pelvic portions. No residual urine or other evidence of disease of lower urinary tract.

Comment.—The stone formation was most likely secondary to the megalo-ureter.

Case 6.—A. B., male, aged 22 months.

Complaint.—Fever; ill-health; pyuria.

Excretion urograms: Poor definition and function on both sides.

Instrumental pyelo-ureterograms: Left ureter dilated and looped so as to reach outer border of left iliac fossa. Right ureter moderately dilated but not looped.

Treatment.—Left ureter shortened and straightened by excision of about 3 in., and reimplantation of remainder into bladder.

Result.—Improvement in general health; urogram four years later showed good drainage from left ureter to bladder.

Megalo-ureter from bilateral early ureterocele.

Case 7.—A. W., male, aged 33.

Complaint.—Attacks of loin pains and blood in urine.

Cystoscopy: The intramural portion of each ureter represented by a well-defined plateau with ureteric orifice on anterior superior edge.

Urogram: Moderate dilatation of both ureters.

Treatment.—Slitting of orifices by high-frequency cutting through cystoscope.

Result.—Disappearance of plateaux and symptoms.

Two cases of megalo-ureter due to unilateral ureteral stricture.

Case 8.—D. S., female, aged 35.

Complaint.—Attacks of right-sided renal colic over several months.

Instrumental ureterogram demonstrated a stricture in right ureter in pelvic portion about 2 in. below pelvic brim, with ureter dilated to diamter of ¾ in. above.

Treatment.—Division of ureter above stricture and reimplantation of ureter into bladder.

Result.—Cessation of symptoms and absence of dilatation of ureter as shown by urogram nine months later.

Case 9.—A. F., male, aged 49.

Complaint.—Attacks of fever and pyuria for several months.

Excretion urogram : Pelvic portion of right ureter between brim of pelvis and bladder dilated to diameter of 1 in.

Treatment.—Division of ureter above dilatation and reimplantation into bladder.

Result.—No further attacks (nine months after operation).

Mr. A. Wilfrid Adams : Miss D. K., female, aged 17, on 15.1.40 gave a history of recurring pain in left loin and frequency for two years. She had not been to bed for it till last few weeks. Dyspepsia had preceded these symptoms.

January 1940 : Intravenous pyelography shows moderate bilateral stasis, which is maximal near the bladder and the ureterograms ¾ in. in diameter. The rest of the ureters and renal shadows are about twice the natural size. Pre-cystoscopic urine was healthy. Pyelography was followed by fever, oliguria, heavy pyuria, and left renal colic, the last persisting after the other features but without appreciable renal swelling. Her suffering compelled exploration 3.3.40, after uneventful catheterization of left ureter. The bladder showed slight general cystitis and a few submucous hæmorrhages. The kidney showed no lesion when exposed but, as a desperate measure, denervation of the renal artery was done with dramatic cure of the symptoms up to date. On 8.4.40 the urine shows *B. coli* infection.

Ætiology.—The cause of ureteric dilatation remains obscure, for the cystitis is a trifling feature. Primary achalasia of ureteric outlets suggests itself as a factor and the ready cure of her renal colic by peri-arterial sympathectomy lends colour to this idea.

P. B., female, aged 29. Mega-ureters shown on intravenous urography (see p. 593)

Miss P. B., female, aged 29, came on 23.10.39, troubled with frequency (D.14, N.5) for four years and mild ache in left loin. Left renal colic occurred once—a year ago. She was quite cheerful and it was astonishing to find severe diffuse cystitis with ulceration and shaggy granulations. On 8.12.39 grossly dilated and tortuous terminal 4 in. of ureters showed on intravenous urography (*see* fig. p. 592). Renal pelves appeared normal, catheters passed freely, and the R. and L. urines each proved healthy on pathological examination. In the bladder sample were pus and rich growth of *B. coli*.

Three months later, 4.3.40, she stated: "Life is now worth living", thanks to the amelioration in dysuria. However, the ureterograms remain unaltered. Guinea-pig inoculation proves negative.

Ætiology.—Can the mega-ureters be fairly explained by compression of the intramural ureters by the grossly inflamed bladder walls? Such a view seems questionable owing to the rarity of such findings despite frequency of heavy cystitis. Pure achalasia need not be invoked as uretero-vesical spasm might reflexly be provoked by the cystitis.

Mr. Clifford Morson: Any acute infection of the upper urinary tract produces temporary megalo-ureter. The dramatic results sometimes claimed for presacral neurectomy are due to a decrease in the degree of infection. Involution of a dilated ureter due to inflammation is often rapid. The case recorded by Ogier Ward and quoted by Mr. Currie as an example of the value of presacral neurectomy is far from convincing. If this operation is to be accepted as a justifiable procedure it must be demonstrated beyond all shadow of doubt that previous to the treatment no infection and no mechanical obstruction were present. The clinical research on the effect of ureteric transplantation into the large bowel upon a dilated ureter and kidney shows that following the removal of the cause, inflammatory or obstructive, the reduction in the size of the ureter, pelvis and calyces is rapid.

The President: I was interested to hear Mr. Currie's reference to inflammation as a cause of megalo-ureter and I should like to cite two illustrative cases. They were both females and each suffered from a very acute cystitis of the alkaline phosphate-encrustation type. The first, aged 42, failing to respond to all recognized forms of simple treatment had eventually to be drained suprapubically. Excretion urography revealed bilateral hydronephrosis and hydro-ureter to a marked degree, the cause of which was obscure. After draining I sent her back to her home in Penzance with instructions that the tube was to be kept in for two months and washing with dilute acetic acid to be continued. On her return to hospital ten weeks later the cystitis had resolved and the upper urinary tract showed no radiographic abnormality whatsoever. The second case, a girl of 18, admitted to hospital with the diagnosis of bilateral renal tuberculosis, also showed very marked bilateral hydronephrosis and hydro-ureter. The cystoscopic picture was entirely unlike tubercle, and tubercle bacilli could not be found. The prontosil group failed to relieve. The Munro system of continuous bladder lavage with 0·5% increasing to 1% acetic acid lotion was established and now, after a six weeks' course, the hydronephroses and hydro-ureters are approximately half the former size (skiagrams shown).

Sterile Pyuria

By Thomas Moore, M.S.

Inflammatory reaction is essentially the same no matter in which part of the body it occurs. The vascular and cellular changes lead to the formation of an exudate which may eventually reach a free surface. In addition to inflammatory cells it contains in organismal lesions the causative bacteria. Thus in the urinary tract examination of the urine is an excellent index of the presence of inflammatory disease which has reached the mucous surface. Cultural examination of the urine will isolate the organism concerned. In some cases, however, although the urine contains many pus cells, no organisms can be obtained. It is with such cases that this paper is concerned and is based on a study of 78 cases of sterile pyuria.

On an ætiological basis these cases can be divided into three main groups: (1) Non-infective, (2) infective with organisms demonstrable on direct microscopical examination of the centrifuged urinary deposit but the urine is sterile on culture, (3) infective cases in which no organisms can be demonstrated in the urine by any method. Each group can be further subdivided according to the uderlying disease (*see* Table I).

The recurrent trauma of a calculus in the urinary tract may lead to sterile pyuria. Infection, however, usually supervenes sooner or later. There were also in this series nine cases of toxic change in the kidneys which led to pyuria without organismal invasion of the urinary tract. As a general rule, however, in acute nephritic conditions hæmaturia and the presence of casts overshadow the pyuria.

TABLE I.—STERILE PYURIA. 78 CASES.

	Cases
I. *Non-infective.*	
Urinary calculi	20
Toxic disease (nephritis)	9
II. *Infective* (Organisms on microscopical examination of centrifuged urinary deposit).	
Resolving infections of urinary tract	2
Faulty technique	4
Urinary tuberculosis	24
III. *Infective* (No organism on microscopical examination of centrifuged urinary deposit).	
Resolving infections of urinary tract	9
Prostatitis	5
True abacterial pyuria	5

The infective group forms an interesting study. In bacterial infections of the urinary tract during the later stages the organisms present in the urine have been so altered by the tissue reactions or by antiseptic treatment that they may fail to grow. There were two such cases in this series. In four other cases the failure of organisms demonstrable in the urine on microscopical examination to grow on culture media was due to faulty technique. There was a long period of delay between the collection of the specimen and the bacteriological examination during which the organisms had presumably died. 24 cases in this group were due to the most common cause of sterile pyuria—viz. urinary tuberculosis.

The most interesting cases are those which fall into the last group. In nine cases bacterial infections of the urinary tract had been overcome but the inflammatory cells had not, at the time of the examination, disappeared from the urine. Within a short time pyuria in these cases disappeared. Five cases were suffering from subacute prostatitis. In this disease it is possible for inflammatory changes at the periphery of the gland and the base of the bladder to be due more to the toxins than to the bacteria themselves, so that sterile pyuria may result. The method of taking the specimen of urine in these cases is of some importance. That obtained by catheterization is more likely to be sterile than that collected under sterile precautions by spontaneous expulsion. When the urine is collected by the latter method after prostatic massage, the causative organism can usually be isolated. There were three male patients aged 17, 30, and 35 years respectively found in the hospital records who for a few weeks had complained of frequency of micturition, dysuria and terminal hæmaturia whose urine contained many pus cells but was sterile on culture. In no case had an attempt been made to isolate the causative organism by prostatic massage. I believe they were all suffering from prostatitis and in one this may have been gonococcal in origin as there was a recent previous history of urethral discharge. They were all treated with simple urinary antiseptics and apparently made a complete recovery. Although in most cases of prostatitis the organism can be recovered after massage, in two in this series with pyuria all attempts to isolate the organism failed. Both cases, however, rapidly resolved on sulphanilamide therapy. Although no case occurred in this series syphilis of the urinary tract leads to sterile pyuria, but the spirochætes can be demonstrated by special methods.

The most important type of sterile pyuria is true abacterial pyuria. This disease is much more common than is usually recognized. The five cases included in this study, however, give a false impression of its incidence; only three occurred together with 73 other cases of sterile pyuria in one hospital during the last three years, the other two cases were seen in another hospital and are included for completeness. Before discussing the disease in more detail a brief account of each case will be given.

Case 1.—Unmarried female aged 42. Six months' history of great frequency of micturition and terminal urethral pain starting a few days after a chill. Had been in the medical wards on two occasions and received the usual medicinal treatments without any improvement in the symptoms. There was no history of venereal disease.

On examination.—A healthy female. Pulse-rate and temperature normal. No abnormality was found on complete clinical examination. Wassermann reaction was negative.

Urine contained many pus cells but no organisms were seen on microscopical examination of the centrifuged deposit. It was sterile on culture.

The plain X-ray examination of the urinary tract revealed no abnormality.

Excretion urography showed good function on both sides but there was definite dilatation of both ureters and pelves (fig. 1). The right pelvis was of a balloon type.

Cystoscopy revealed normal bladder except for slight general erythema. Both ureteric orifices were normal. A number 5 F. catheter passed up each side easily to 30 cm. and drained freely. Both urines contained many pus cells but no organisms and were sterile on culture. The urine from the bladder and both kidneys was shown to be free from tubercle bacilli by guinea-pig inoculation. A diagnosis of true abacterial pyuria was made. The patient was treated by intravenous injections of 0·15 grm. of novarsenobenzol at intervals of five days. Altogether four doses were administered. The symptoms began to improve immediately. By the completion of the treatment the patient was symptomless and the urine was free from cells. There has been no recurrence.

FIG. 1.—Excretion urogram. *Case* 1, showing dilatation of pelves and left ureter.

Case 2.—Female, married, aged 64. Frequency of micturition, terminal urethral pain and occasional hæmaturia for twelve months. No history of venereal disease.

On examination.—Good general condition. No abnormality was detected on complete clinical examination. Wassermann reaction negative.

Urine contained many pus cells. No organisms seen on microscopical examination of centrifuged urinary deposit. Sterile on culture. Guinea-pig inoculation was negative for tubercle bacilli.

Plain X-ray examination of urinary tract and *excretion urography* showed definite dilatation of both pelves and ureters.

Cystoscopy showed slight diffuse inflammatory changes in the bladder. The trigone and the area immediately surrounding it was the site of superficial ulceration which in parts was covered by white fleshy and papilliferous debris. A specimen of this tissue was taken for histological examination. It was entirely necrotic. The affected area was carefully fulgurated. Treatment was repeated in three months. The patient did not obtain any benefit. A course of novarsenobenzol was started. 0·15 grm. was administered at five-day intervals for four doses. The symptoms rapidly disappeared and the urine became normal.

Further cystoscopy three months later showed the bladder to be normal except for scarring at the site of the previous ulceration. There has been no recurrence of symptoms.

Case 3.—Unmarried female aged 50. Complained of constant burning pain across the lower abdomen and great frequency of micturition for five years. There was terminal urethral pain and occasional hæmaturia. No history of venereal disease. All medical treatment and complete urinary investigation failed to relieve the symptoms.

On examination.—Healthy-looking woman with a normal temperature and pulse-rate. No abnormality was detected. Wassermann reaction negative.

Urine contained numerous pus cells but no tubercle bacilli or other organisms: sterile on culture. Special cultures for tubercle bacilli were also negative.

Plain X-ray examination of the urinary tract showed no abnormality.

Excretion urograms revealed excellent function on both sides and normal appearances on the left. There was some dilatation of the right ureter and one or two small but constant filling defects in it (fig. 2).

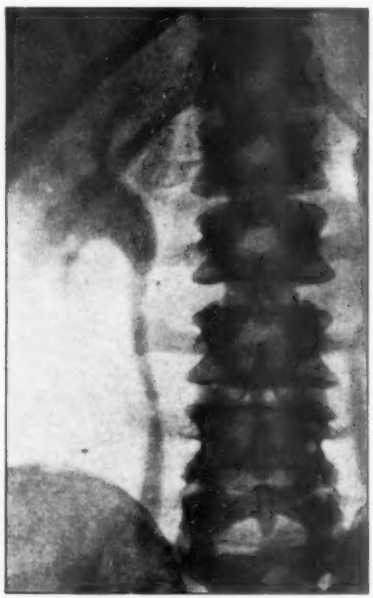

FIG. 2.—Excretion urogram. *Case* 3, showing filling defects in right ureter due to ureteritis follicularis.

Cystoscopy showed a much diminished bladder capacity and diffuse inflammatory changes most marked on the lateral walls and dome. Both ureteric orifices were normal. The symptoms were relieved for a week or two on two occasions by bladder distension but the patient was only completely cured by a course of novarsenobenzol. 0·3 grm. was administered at weekly intervals for four doses. The symptoms began to subside and the urine to clear immediately. At the end of the course the patient was entirely cured and the urine free from cells. There has been no recurrence.

Case 4.—A male aged 36. Six weeks' history of frequency of micturition and occasional terminal hæmaturia. Never had venereal disease.

On examination.—Good general condition. Temperature and pulse-rate were normal. No abnormality was detected on clinical examination. Wassermann reaction was negative.

Urine contained many pus cells, but no tubercle bacilli or other organisms. It was sterile on culture.

On rectal examination definite swelling of both lobes of the prostate with some areas of inflammatory induration could be felt.

The prostatic secretion contained a marked excess of white blood corpuscles. A diagnosis of subacute prostatitis was made and patient given a full course of sulphanilamide therapy (15 grm.) in one week, with no effect. Urine taken after prostatic massage contained many pus cells but no organisms.

Guinea-pig inoculation proved tubercle bacilli absent.

Cystoscopy showed scattered areas of erythema and œdema in the bladder. Both ureteric orifices were normal. Patient's symptoms were relieved for a few days only by the cystoscopy. An intravenous injection of 0·3 grm. of neoarsphenamine was given on four occasions at intervals of seven days. Immediately the symptoms began to improve and the pus cells to disappear from the urine. When the treatment had been completed the patient was symptomless and the urine free from cells. There has been no recurrence.

Case 5.—Male, aged 26. For seven weeks had complained of extreme frequency of micturition and pain at the end of the penis after urination. There was also occasional terminal hæmaturia. No history of venereal disease.

On examination.—Good general condition. Temperature and pulse-rate were normal. No abnormality was detected on clinical examination. The external genitalia were normal. Wassermann reaction was negative. Blood urea estimation—26 mgm. per 100 c.c.

Urine contained many pus cells, no tubercle bacilli or other organisms. It was sterile on culture.

On rectal examination prostate was felt to be definitely slightly swollen and boggy. Prostatic secretion contained a marked excess of leucocytes. Patient was given 15 grm. of sulphanilamide in the course of one week without any improvement in the symptoms or change in the urinary findings.

Plain X-ray examination of the urinary tract and excretion urography showed no abnormality.

Cystoscopy revealed diffuse inflammatory changes in the bladder most marked at the base. Both ureteric orifices were normal. Patient was given two doses of 0·3 grm. of novarsenobenzol at intervals of five days. The symptoms quickly subsided and the urine became free from cells. There has been no recurrence.

In claiming that the urine from these cases was sterile reference must be made to the bacteriological technique employed. Cases 1, 2, and 3 were investigated by the ordinary routine examination used in the hospital. This consisted of plotting samples of the centrifuged urinary deposit on plates of MacConkey's medium and on agar plates. In Cases 4 and 5 when the urine was found to be sterile by this method, blood agar plates were used as well and in all investigations samples were kept under aerobic and anaerobic conditions. Specimens of urine from these cases were examined thus on numerous occasions. The results were always negative except once in Case 4 when a facultative anaerobe later identified as the *Bacillus xerosis* was isolated. This was undoubtedly a contaminant.

In addition in these cases bulk cultures, in which ½ c.c. of urine was placed in a tube of glucose peptone broth, were carried out. This is a gross method and organisms can often be grown by it from the urine of healthy subjects. In Case 4 on one occasion a culture of the *Streptococcus viridans* was obtained by this method. Unfortunately we were not able to keep it alive sufficiently long to be able to test its pathogenicity to animals.

These cases then are examples of true abacterial pyuria, which is a definite and specific disease caused by an unknown agent. In Case 1 both upper urinary tracts were mainly affected ; in Case 2 the bladder was the main site of the disease ; in Case 3 the bladder and the upper urinary tract on one side were affected ; while Cases 4 and 5 are examples of the disease affecting particularly the bladder and prostate.

The diagnosis of this disease is important as it is very liable to be mistaken for urinary tuberculosis and surgical treatment undertaken. In view of the excellent results of adequate medical therapy such a course is a tragedy for the patient. Faltin in 1909 was the first to draw attention to cases of sterile pyuria in which tuberculosis could be excluded. He thought that gonococcal prostatitis might account for some of them. 30 cases were reported by Runeberg (1921) in 10 of which nephrectomy had been carried out. Histological examination showed no evidence of tuberculosis. Peters (1922) carried out nephrectomy in 5 out of 15 cases. Microscopical examination showed non-tuberculous

inflammatory changes but no organisms. That the disease was a specific entity and quite unrelated to urinary tuberculosis, although the ætiology was not clear, was first suggested by Söderland (1921) who reported three cases. Vintici and Constantinescu (1929) divided sterile pyuria into two types—false, which could be a stage of various infections of the urinary tract and true abacterial pyuria of which they had never seen a case. In 1933 Wildbolz addressed the French Congress of Urology and stressed the resistance of the disease to ordinary forms of treatment but its truly miraculous cure by the intravenous administration of a novarsenobenzol preparation. Since this time the disease has become more widely known and observations on it have been published by Briggs (1935), Cook (1936), Schaffhauser (1937), Houtappel (1939), Weytlandt (1939), and Moore (1940).

Ætiology.—The possible causation of the disease will be considered under the following headings: (1) Bacteria, (2) toxins, (3) syphilis, (4) fungus infection, (5) ultramicroscopic virus. Although the characteristic feature of the disease is the absence of bacteria from the urine, there is a little suggestive evidence that staphylococci or streptococci may play some part in the ætiology, which must be considered. Runeberg (1921) found staphylococci imprisoned in the cortex on histological examination of the excised kidneys in some of his cases. He suggested that the inflammatory products exuded from this area into the renal pelvis without the bacteria. The fact also that novarsenobenzol preparations are of some value in the treatment of staphylococcal infections of the urinary tract lends support to the view that some type of staphylococcus is the cause of abacterial pyuria. However, the inability of all workers to isolate staphylococci from the urine and the different clinical picture seen in true staphylococcal urinary infections, especially the marked constitutional effects so lacking in true abacterial pyuria, leave little doubt that staphylococci play no part in the ætiology of the latter disease. Schaffhauser (1937) isolated a non-hæmolytic streptococcus from the urine of three of his last four cases of abacterial pyuria by using Rosenow broth medium. The organism was not pathogenic to animals. The fact that he was able to produce a subacute pyelitis in dogs by intrapelvic injection of the urinary deposit rather suggests that the organism was a contaminant. A similar contaminant was isolated on one occasion only from one of our cases. We did not use Rosenow medium as it was considered that an organism which would grow on it would do also on the media we employed.

It has been suggested that true abacterial pyuria is caused by the excretion of toxins. Cook (1936) reported cases which responded in the ordinary way to novarsenobenzol but relapsed and were not finally cured until in addition a focus of sepsis had been removed. The disease, however, is much more like a true infection of the urinary tract than a toxæmia. In no case in this series was a septic focus present.

In those rare cases of syphilitic infection of the urinary tract sterile pyuria occurs. The spirochætes, however, can be demonstrated in the urine by the dark ground illumination and by special culture. According to Wildbolz (1937) such examinations are always negative in true abacterial pyuria. The Wassermann reaction was negative in the five cases I investigated.

There is no evidence that a fungus infection is responsible for true abacterial pyuria. In such cases the organisms are easily demonstrable in the urine. The constantly negative bacteriological urinary findings in true abacterial pyuria lend strong support to the view that an ultramicroscopic virus is the cause of the disease. The first evidence for such an ætiology for any condition is always of a negative character. Schaffhauser (1937) has proved that the disease can be transmitted to dogs by injection of the urinary deposit. If this can be shown to be true for the specially filtered urine, positive evidence in favour of the ultramicroscopic virus theory of the causation of the disease will have been secured.

Pathology.—Our knowledge of the pathological changes comes from the histological examination of kidneys excised in the mistaken belief that a tuberculous infection was present. All reports stress the absence of parenchymal changes. The inflammatory changes are confined to the pelvis and ureter. The mucosa is thickened, œdematous and somewhat red and covered by flakes of fibrin. In some cases there are present small rounded swellings in the mucosa—the so-called pyelitis and ureteritis follicularis. Microscopical examination shows infiltration of the submucosa with inflammatory cells which in parts are collected into follicles.

Symptomatology.—The onset is either sudden or insidious. The symptoms are those of severe cystitis. The ureteric and pelvic changes rarely give rise to symptoms and

in spite of the widespread inflammation there are no general constitutional effects. According to the literature the disease is most common in young male adults but in my experience middle-aged females are often affected.

On clinical examination no physical signs can be elucidated. The urine contains many pus cells but no organisms can be demonstrated by direct microscopical examination or culture. When the ureter and renal pelvis are affected excretion urography may show them to be dilated. Occasionally small filling defects may be seen in the urogram due to pyelitis or ureteritis follicularis. In such cases differential renal functions tests show some diminution of function on the affected side. Cystoscopy reveals diffuse inflammatory changes in the bladder and a markedly reduced bladder capacity. There are none of the characteristic appearances of tuberculous cystitis. Examination of the urines obtained by ureteric catheterizations demonstrates if any part of the upper urinary tract is affected.

Diagnosis.—One disease which must be excluded is urinary tuberculosis. In the past cases of sterile pyuria were always diagnosed as being due to urinary tuberculosis whether the bacilli could be demonstrated in the urine or not. Thus as late as 1913 Rovsing was stressing the then accepted view that in about 10% of cases of urinary tuberculosis the organisms could not be demonstrated in the urine but the diagnosis was still valid. To-day in about 90% of cases the bacilli can be demonstrated in the urine by microscopical examination of the centrifuged deposit alone. In negative cases special cultures sometimes give a positive result. In all cases of active disease the bacilli can be demonstrated by guinea-pig inoculation of the urine. The diagnosis of urinary tuberculosis should not be made if the bacilli have not been demonstrated in the urine.

Another disease which may cause a little difficulty in diagnosis as it is sometimes associated with sterile pyuria, is subacute prostatitis. However, by examination of the prostatic secretion or of the urine obtained after prostatic massage the causative organism can be isolated, except in those cases in which the prostatitis is part of a true abacterial infection.

In any case where the diagnosis is uncertain the therapeutic test is a safe and valuable aid.

Treatment.—The disease is resistant to all ordinary forms of treatment. It clears as if by magic when intravenous injections of novarsenobenzol are given. A dose of 0·3 grm. should be administered at weekly intervals up to four doses if necessary.

I must express my indebtedness to Dr. Russell Herring, Acting Director of the Clinical Laboratory, of the Manchester Royal Infirmary, for allowing me access to the records and for the bacteriological investigations.

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Mr. TERENCE MILLIN stated that in his experience these cases of "Sterile Pyuria" were due to a staphylococcus. By perseverance he had not yet failed to isolate this organism in every such case. It might be necessary to examine several specimens of urine, but either in centrifuged deposit or on culture, using the trypsin blood agar medium recommended by Dr. John Bodman, the staphylococcus had been found. Mr. Millin had not been so fortunate in curing all his cases dramatically with three injections of N.A.B. Some did respond in very gratifying manner; others did better on uleron; in one case a nephrectomy had been necessary for unilateral pyuria, where uleron, N.A.B., and every other antiseptic tried, had failed. This kidney had been sectioned for evidence of tuberculosis, and cultures from the cut surface of the kidney at operation had grown staphylococcus.

DISCUSSION ON RECENTLY INTRODUCED BRITISH DRUGS AND THEIR USES IN UROLOGY

Dr. N. S. Finzi : I have recently used " uropac " in two cases [photographs demonstrated] and you will note that the shadows are excellent, being at least as good as uroselectan, if not better. It is claimed that this compound is exactly the same as uroselectan.

Cases taken at Friern Hospital with " pyelectan " show good shadows, but they are not equal in these particular cases to the " uropac " shadows. This may be merely chance as the number of cases of both are so few.

I saw one of the uropac injections given and there was no pain after the injection which was done by Mr. Hermon Taylor. The other " uropac " case had very slight pain in the arm and shoulder after the injection.

Dr. E. W. H. Shawcross : Recently some 15 cases of intravenous pyelography have been carried out in my Sector Hospitals, using the drug pyelectan. The results have been quite successful but the shadow of the pelves and calyces in these few cases do not appear to be as dense as those obtained by the majority of cases using uroselectan, though the formula is given as the same for the two drugs. We have not found any advantage in taking five minutes over the injection as suggested by the makers ; the time taken for the injection of the 20 c.c. being about one minute. Patients appear to get more pain in the shoulder when the drug is injected than with the use of uroselectan, but this pain does not appear to be severe and has always passed off in a few minutes. In the one case where the injection was given very slowly the pain appeared to last longer. In none of my cases have I obtained such good contrast as Dr. Finzi has obtained in the films he has just shown using uropac.

Dr. F. Barnett Mallinson : The barbiturates are undoubtedly of particular value in many urological procedures.

The barbiturates which concern us can be divided into anæsthetics and basal hypnotics. Of the anæsthetics: First, the oldest and the original one is evipan. It is well known and tried, if somewhat overshadowed by the more modern thiobarbiturates ; Second is eunarcon, which has been tried over here but is inferior to evipan and not without danger. A third is narcogen ; this does not seem to have made any headway in this country. Fourthly there is the American drug venesetic ; this is very similar to the British drug pentothal, both of them being thiobarbiturates, that is containing a sulphur radicle. It is perhaps not quite so efficient and a little more expensive to use. Lastly comes pentothal which is now generally accepted as the most reliable and efficient intravenous anæsthetic at the present time.

A new British drug which is being developed is cyclonal, but it is not yet marketed.

An interesting possibility is English evipan. I understand that three British firms intend to make it. We shall then have both English evipan and English pentothal (the latter has been on the market for about two years) from which to choose. These two products are the only ones which have contributed a real advance to intravenous anæsthesia.

With regard to the basal hypnotics the position is much the same. Their variety, however, is endless. The chief British ones are nembutal and soneryl.

[This contribution has been summarized owing to pressure of space.]

Mr. Millin thought that the urographic media, uropac and pyelectan, were quite as good as uroselectan and abrodil, and he had not noted any more marked shoulder pain with their use. He had also employed them, diluted with twice the volume of distilled water, for ascending pyelography, urethrography, and in 1 : 8 dilution, for cystography.

Mr. Heritage said that in prostatic surgery he aimed at the minimum amount of anæsthetic and a rapid return to consciousness after operation. These were admirably met by the use of pentothal sodium for induction, and maintenance by nitrous oxide and oxygen through the McKesson apparatus. Where added relaxation was required further injections of small quantities of pentothal were given. In skilled hands this proved adequate for all forms of prostatic surgery, especially a modified Harris technique which was the method of choice. Bleeding from the prostatic cavity was free, and could therefore be controlled. This method of anæsthesia had been used for all cases during the last five years, and although the patients' ages ranged up to 84 years, no immediate or remote disadvantages had been encountered.

The method was not one for the occasional user, as all depended on the judgment of the anæsthetist and the amount of experience he had gained of intravenous anæsthesia.

Section of Surgery

President—V. ZACHARY COPE, M.S.

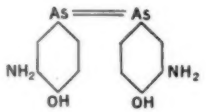
[*April* 17, 1940]

Chemotherapy in Surgery

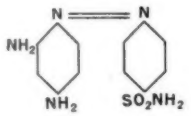
By NORMAN C. LAKE, M.D., D.Sc., M.S., F.R.C.S.

CHEMOTHERAPY as such may be said to have been born when Ehrlich produced such materials as salvarsan and other organic compounds of the metals which have revolutionized the treatment of spirochætal and protozoal diseases.

The structural formula of salvarsan is not so unlike that of some of the new anti-streptococcal compounds. Salvarsan is dihydroxy-diamino-arsenobenzol which is represented graphically by the formula :—



Now the original commercial antistreptococcal preparation was prontosil, the structural formula of which is



In the interval between the development of these two compounds many attempts were made to discover materials having an effect upon cocci and bacilli. The dyes naturally attracted attention since many of them were obviously "fixed" by organisms, as is demonstrated by the fact that they so readily dye, or stain, the organisms on our microscope slides. There is, indeed, a very definite relationship between the "fastness" of a dye for the colloidal fibres of which most of our fabrics are made and its bactericidal activity. A fast dye may thus be suspected of bactericidal powers ; Hörlein in 1910 found that the fastness of azo dyes was greatly increased by the incorporation of a sulphonamide group.

Other materials have of course been used clinically, for instance acriflavine or mercurochrome intravenously, but in general the results have not been very impressive.

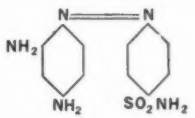
In 1913 Eisenberg showed that *in vitro* the azo dyes had a relatively powerful bactericidal action, but his attempts to apply chrysoidin for this purpose in the body were unsuccessful. In 1919 Heidelberger and Jacobs at the Rockefeller Institute found that sulphamido-azobenzene compounds had considerable bactericidal powers, but again this discovery led to no practical application.

Later Mietzsch and Klarer discovered still more active compounds having the azo and sulphonamide groups in the benzene ring. The British Drug Houses have produced such materials as S.U.P.36, &c., for many years. These are symmetrical urea products, but they also contain amino and sulphonate groups.

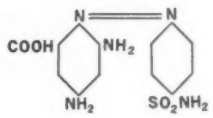
It was not until 1935, however, that Domagk showed that the azo compounds with a sulphonamide group have a definite therapeutic effect upon the experimental streptococcal septicæmia of mice, and a series of somewhat similar products was developed. These, however, were not devoid of toxic effects. A year later it was found that the azo arrangement was not essential, but that the colourless and comparatively simple compounds containing a sulphonamide group were equally or even more active. It was further suggested that when products of the azo dye type entered the body a breakdown occurred, liberating simpler substances of the amino-sulphonamide type, which alone are responsible for the bactericidal activities.

At the present day we have available a large series of products of a similar nature the structural formulæ of which are here given :—

PRONTOSIL

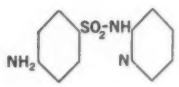


RUBIAZOL



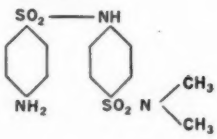
SULPHANILAMIDE (PRONTOSIL ALBUM)

SULPHAPYRIDINE (M & B 693)

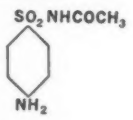


These are chiefly in use against streptococcal and diplococcal infections. In addition certain products having a different side linkage have been evolved for which antistaphylococcal action is claimed :—

ULERON



ALBUCID



There are many synonyms for sulphanilamide which must not deceive us ; some preparations have additional side chains for which special properties are claimed.

It would probably be a fair summary of the present position to say that the experiments prove (*a*) that these compounds have a powerful effect against hæmolytic streptococcal infections, (*b*) that some of them are particularly active against the diplococcal group of organisms, (*c*) that one or two are effective against staphylococcal infections, but the others are inactive, (*d*) in gas gangrene, infections with *Cl. welchii* and *Cl. septique* yield to certain of the preparations, but that the *Cl. œdematiens* is very resistant to all, (*e*) all are without effect upon the virus diseases.

The practical surgeon will ask how these experimental results fit in with the clinical results. I have attempted to answer this important question partly from chemical and experimental reports but chiefly as a result of clinical observations. The very diversity of a

general surgeon's work renders it difficult to collect a large enough series of any individual condition to make an impressive statistical and comparative study, but the varying experiences which it provides over a wide range of different conditions may enable him to reach some worth-while conclusions.

First with regard to the specificity of the various products. Here my clinical results agree fairly closely with the experimental ones, and have led me to believe that they are specific in their action, in some instances remarkably so. Plain sulphanilamide, under its numerous synonyms, has proved to be very effective against hæmolytic streptococcal infection ; it has been of little value against other more resistant streptococci, particularly of the fæcalis type. I have not found it to be of use in staphylococcal infections. As an instance of this I may record ten cases of violent infection of the fingers and hand, all associated with lymphangitis, enlargement of glands and severe general symptoms, eight yielded to sulphonamide but two showed no response. Bacteriological investigation showed that these two were due to the *Staphylococcus aureus* although clinically they exactly resembled the other streptococcal cases.

This specificity of action is often demonstrated in cases of mixed infection when the sensitive organisms are destroyed while the others may get a firmer footing. In cases of cystitis and pyelitis the *Streptococcus fæcalis* remains after other organisms have been cleared up by chemotherapy. At the Mayo Clinic they are now trying sulphathiazole and sulphamethylthiazole, for these cases with, it is claimed, remarkable success. It has, of course, not been suggested that the sulphanilamide compounds are of value in bacillary infections (although claims have recently been advanced for their use in anthrax) and corresponding to this I have noted in some cases of highly infected wounds and sinuses that the pyocyaneus organism is one that gets a hold when the more virulent cocci have yielded to treatment.

Cases of erysipelas have responded well to sulphanilamide, as did also the cases in a small outbreak of post-operative wound infection traced to a hæmolytic streptococcus from the throat of a nurse. The nurse herself, however, was not cleared of the organism even after several courses of various chemotherapeutic agents had been tried. This suggests that where the natural powers of resistance have reached a balance with the invading organisms over a period, chemotherapy cannot be relied upon to upset that balance.

I have had the opportunity of treating a few cases of streptococcal infections of large joints in this way, but, although I have little doubt that the general effect was excellent, in all cases it was necessary to adopt surgical measures in the form of repeated aspirations and subsequent open drainage. One case, of four, in which knee-joint infection was secondary to a severe diabetes, died after the infection had spread to the intermuscular cellular tissues of the thigh, probably through the needle punctures of the earlier aspirations.

Two cases of submaxillary cellulitis responded fairly well, additional surgical treatment being necessary ; in many of these cases there is undoubtedly a very mixed flora present so that they are not good examples of antistreptococcal action.

The results of this treatment in throat cases, in gonorrhœa or in infections, post-operative or other, of the lungs have been already widely reported. But the general surgeon is concerned with infections of the pleura. It is to be expected that the exhibition of sulphanilamide and especially of sulphapyridine in lung infections will greatly diminish the incidence of pleural infections. In my experience in cases of empyema these products form a very useful addition to, but not usually a substitute for, surgical treatment. The problem of empyema raises a question of general interest, namely whether these materials can be expected to have much action upon closed collections of pus. It is easily arguable that substances circulating in the blood-stream cannot reach the organisms in a cavity, and this conclusion is widely accepted, but it must not be forgotten that the active organisms are those present in the living walls of the cavity where they come under the influence of exudates from the capillaries and, therefore, under the influence of such chemicals as may be present in the blood. That such influences may be very effective in combating the organisms is occasionally demonstrated under entirely natural circumstances by the formation of abscesses the pus in which is sterile, and I believe that a similar effect occurs frequently with chemotherapeutic treatment. I have certainly seen smaller collections of streptococcal pus disappear with

the treatment; where the amount of pus has been large, as in empyema or knee-joint infection, it has been necessary to supplement the treatment by active surgery, as we have already seen. In the case of massive infection in cavities it is feasible that, even if the active organisms in the wall of the cavity were destroyed, reinfection from the pus would occur. Some clinical observations lend support to this view.

The results have been less remarkable in staphylococcal infections. Outstanding among staphylococcal infections is acute osteomyelitis. In view of the specific action of the chemotherapeutic materials, it is not surprising that both sulphanilamide and sulphapyridine should have been found to be of little value. I used them in the early days upon several cases, and even recently in two cases where I wrongly thought that I was dealing with a streptococcal bone infection, proved subsequently to be due to a very virulent *Staphylococcus aureus*. In all these no obvious clinical results were obtained. With uleron, however, I have had some happy experiences. Rubiazol and albucid are said to have a similar effect, but I have no personal experience of them in osteomyelitis.

All these substances are sulphonamide derivatives and possibly the expert chemist might be able to tell us what particular side linkage gives the products this antistaphylococcal action; for my own part I have to rely upon clinical observations. It is true that there are many grades of severity in osteomyelitis and that the blood-stream infection varies greatly, so that the clinician may be deceived when dealing with comparatively small groups of cases. Even when due allowance is made for this, I feel that in uleron (and possibly in the others mentioned) we have a very powerful remedy in this disease. When given in the early stages, on a definite diagnosis, the signs and symptoms usually disappear in three or four days, and in many of these early cases no need for surgical interference arises. I expected that some of the cases would later show signs of a Brodie's abscess, but so far I have not been able to confirm this. Possibly such a sequel may depend upon the exact site of the invasion of the bone. In other less serious staphylococcal infections both uleron and rubiazol have been employed successfully.

In general each compound appears to have a special activity against certain types of organisms and much less or no action against others. Nevertheless this specific action is not absolute and does not always run along parallel lines for different parts of the body. Thus if we take one particular chemical and make a chart of its relative efficiency upon different organisms invading some tissue in the body, and then make a corresponding record of its efficiency against the same organisms in the urine, the two charts will not of necessity be the same. This is an unexpected and rather paradoxical result for which I am unable to offer a good explanation. I believe, however, that a little light may be thrown upon this problem when we consider the mode of action of these materials, and so we address ourselves to the second question. How do they act?

To answer this it will be necessary to appeal to experimental work. *In vitro* some of the products have a direct bactericidal, or at least bacteriostatic, effect in considerable dilution, but most observers agree that when mixed with deleucocyted blood they have little action. As soon as leucocytes are added the full effect of the chemical is developed. It is clear, therefore, that in some way these products enhance the natural resisting powers of the body. Whether they do this by increasing the phagocytic power of the leucocytes, thus acting like opsonins, or whether by diminishing the vitality of the organisms they render them easy prey for the white cells is at present a matter for conjecture. The fact that long-continued administration is accompanied by a risk of agranulocytosis might tempt us to take the former view, for it is an accepted biological fact that stimulating influences if long continued or excessive often have a reverse inhibiting action. There is, however, also some evidence to show that the vitality of the organisms is seriously diminished by these substances and many have been forced to the conclusion that both factors are at work.

That the natural resisting powers are involved, apart from the leucocytes, seems to be shown by the experimental observations upon gas gangrene infections, when the best results were obtained by a combination of chemotherapy and antiserum. Since this is mainly a clinical discussion I will not pursue this aspect further.

Care is required in answering the next question: Are they sufficiently reliable to replace other long-established methods of treatment? Obviously no general answer can be given to this, but there are some awkward pitfalls into which over-enthusiasm may lead us. Too frequently the natural course of a disease is ignored when claims are made

for new treatments. In dealing with streptococcal infections particular caution is necessary for they are prone, as we all know, to termination by some form of crisis at the end of a few days. In assessing our results therefore we must bear this in mind. Nor must the results obtainable by treatment with antitoxic sera be overlooked, for they are sometimes brilliant. I recall, in my house-surgeon days, an epidemic of post-operative streptococcal infection affecting six cases in a ward. The initial case, a radical mastectomy, died rapidly before a sufficient dose of serum was given, but the other five responded very promptly and all cleared up within a few days. This was, of course, with the old polyvalent antistreptococcal serum ; the newer antitoxic sera are of greater value. On the other side of the balance we must unfortunately place large numbers of cases which have failed to respond at all, probably because the sera are too specific to affect any other than the particular strain of organism for which they are produced.

I have borne all these points in mind when coming to the conclusion that the chemotherapeutic products can in many instances completely replace older forms of treatment, but it may be noted that their exhibition does not mean that other appropriate treatments may not be used in addition. Thus surgical drainage and serum are employed in addition to chemotherapy.

What deleterious effects can they have upon the body? I have seen very few. Minor complaints, such as headache, nausea, lassitude and general malaise, have been frequently observed, while distinct cyanosis and methæmoglobinæmia have been seen in about one case in five. I have no experience of the preventive value of methylene blue in the latter conditions, but as in all instances these conditions appeared to be very transitory phenomena, causing little disturbance to the patient. I have not considered them in any way a contra-indication to the treatment. The more serious state of agranulocytosis is recognized to be associated with the administration of the sulphanilamide products, but I have not met with any cases, though I know of two cases in which it followed prolonged administration. On the other hand I have two cases of chronic conditions in which, following a full dosage of sulphapyridine for five days, a reduced dosage of 1½ grm. was continued for several weeks continuously, with blood-count control. At the end of this period the white counts were between six and seven thousand with 65% and 70% polymorphs respectively. In another case treatment with rubiazol was continued over several months, with, it is true, short intervals, but the white count remained normal. I can offer no explanation why some patients develop agranulocytosis so readily while others are very resistant, but the consensus of opinion is that the method of administration is a factor of importance. The concentration of the drug in the blood should reach its maximum as soon as possible by giving large initial doses ; it should be maintained at this level for a few days only, and further administration should then cease whether or not there has been a satisfactory response. More prolonged treatment should be given intermittently with sufficient free intervals. Many believe that these prolonged administrations defeat their object because the organisms become resistant to the drugs.

To some extent these conclusions give an answer to our final question : Are they safe enough to warrant their use in cases where the nature of the infecting organism is unknown ? Scientifically these compounds should be given for the treatment of the appropriate infections only after bacteriological proof of their nature, but if we keep strictly to this principle we shall certainly deny the treatment to many cases where it may have been of the utmost value. If bacteriological proof can be obtained easily and rapidly this should be done, but in other cases a careful clinical diagnosis should be sufficient to warrant a trial of chemotherapy. Clinical diagnosis can be very deceptive in some cases, but I have no evidence that the cases thus wrongly treated suffered any serious development as a result.

Chemotherapy is of use for other conditions not so obviously within the sphere of application of these products.

The secondary infection associated with discharging sinuses in tuberculosis of bones and joints often yields well to chemotherapy, although the reinfection which almost surely occurs may seem to indicate that such treatment is misapplied. There arise periods, however, in these cases when the secondary infection dominates the picture and at such times chemotherapy will be found useful. I have already mentioned that pyocyaneus infection may become active as the cocci yield to treatment.

In diverticulitis of the colon, apart from major attacks ending in abscess formation, there are recurring attacks of inflammation of less severe character. I have treated a number of these cases chemotherapeutically, usually with rubiazol. The treatment shortens the duration of the attacks and probably prevents many of them from becoming major. The usual dietetic and other régimes are, of course, used in conjunction.

It has been authoritatively stated that chemotherapy has little prophylactic value, the presence of the organisms being necessary for the powers of these substances to develop. This implies a great difference between the invasive and toxic properties of organisms. It is difficult to reconcile this view with clinical experiences, and therefore I have not hesitated to use the new products in this way when a septic operation is contemplated. The number of cases available for study is too small to justify any dogmatic statement, but my impression is that such use is well worth while. This applies particularly to operations upon the colon. I have not used these materials in acute appendicitis, but in the type of appendicular pain in children which follows a tonsillar infection with enlargement of cervical glands, and which is probably due to a real non-obstructive appendicitis, they appear to be very effective.

Finally I will mention two cases of Crohn's disease in which I have tentatively used chemotherapy. Whatever the primary cause of this interesting condition, there must be a well-marked secondary infection which might be reduced in this way. One of these cases ultimately had a surgical resection done for obstruction and is therefore of little value for our purpose, in the other, sinuses were already present and laparotomy, while confirming the diagnosis and allowing of biopsy and bacteriology, revealed such technical difficulties owing to adhesions that the intended resection was abandoned. The subsequent progress of this case treated chemotherapeutically is such as to inspire the belief that the method is worthy of further trial. This case is still under treatment and observation.

[*June* 26, 1940]

The Protection of the Soldier in Warfare

By KENNETH M. WALKER, F.R.C.S.

DURING the last Great War I was lucky enough to create for myself a unique job, which allowed me to wander at will over the Third Army front and study such subjects as the early treatment of the wounded in the trenches, methods of transport back to the casualty clearing stations, and the shock and blood transfusions in the aid post. During that time I kept my eyes open, and in 1918 I made an interesting observation. I became deeply impressed by the frequency with which men in the front line were being killed by tiny splinters of grenade and shell entering the front of the chest, splinters that ripped open the heart, or the roots of the great blood-vessels, and caused almost instantaneous death. Such splinters often had very low penetrating power, and, as the pictures in the daily press showed, many men had had miraculous escapes from death through carrying in a breast pocket such articles as a cigarette case or a New Testament. But for every lucky escape there were a hundred deaths, and since these fatalities rarely reached the casualty clearing stations, or even field ambulances, they passed away unchronicled in medical statistics.

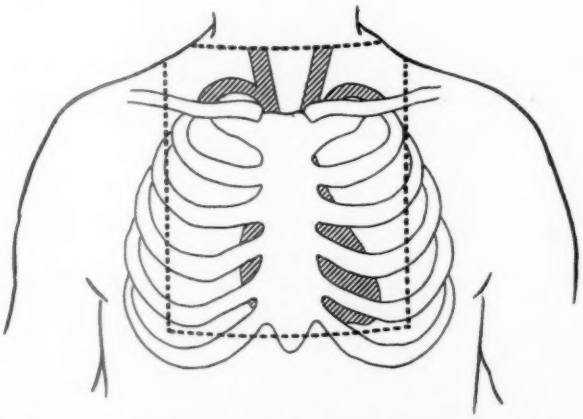


FIG. 1.—Vital area to be protected. In the alert position that portion below the level of the clavicles is covered by the box respirator, but for the protection of the subclavians reinforcement of the straps passing over the shoulders would probably be necessary.

My opinion at that time was unsupported by any figures, but since then I have found confirmation of it. Sauerbach has stated that out of 300 dead examined on the battlefield, 37% showed chest wounds, whilst Loeffler records the slightly lower figure of 29% amongst 469 dead. Now let us go back to the casualty clearing stations. Here we find that chest wounds only made up 3% of the total wounded admitted. The explanation of this discrepancy is simple—the great majority of chest wounds are immediately fatal. Sufferers from them die on the battlefield.

Realizing that the most vulnerable area was, roughly, that which was covered by the box respirator in the alert position (*see* fig. 1), I put up to General Headquarters the suggestion that stationary men, like front line sentries, should carry in a pocket at the back of the respirators a steel plate curved to the front of the chest. By a suitable attachment this plate could be fixed to a wooden handle so as to form an excellent entrenching tool. This memorandum eventally found its way into the hands of an official with wide vision and force, Mr. Winston Churchill. I was recalled from France and informed that I was to be attached to the Ministry of Munitions as Expert in Light Armour. Mr. Winston Churchill had schemes for developing tank warfare enormously in 1919. In such highly mechanized warfare the addition of a little extra weight to the soldier was not an insuperable difficulty. Mr. Winston Churchill wanted the whole subject carefully considered.

If warfare in 1918 was heavily mechanized, that in 1940 is doubly so. Moreover other changes have taken place in this interval. We are now possessed of steels of tensile power immeasurably greater than those we formerly possessed. As a result, the old objection that was invariably brought forward whenever the question of protection was raised, to the effect that the weight that the soldiers had to carry on the march rendered armour impracticable, no longer holds. The man I want to protect does not march; he is carried in a lorry, on a motor bike, on a gun-carriage or in an aeroplane. The weight he would have to support is a third of what would formerly have been necessary.

Precisely what weight would he have to support? That depends on the velocity of the projectile from which it is proposed to protect him. An analysis of the wounded arriving at casualty clearing stations during the last war showed that 61% had been put out of action by projectiles other than the bullet; 58·51% by shell and trench mortar splinters, 2·19% by bombs and grenades and 38·19% by bullets. The following table indicates the velocity of various—mainly German—projectiles:—

Howitzer Krupp, 75 mm.; initial velocity, 1,100 feet per second.

Bursting Velocity.

Range 0 yards	1,640 feet per second
1,000 ,,	1,140 ,, ,, ,,
2,000 ,,	953 ,, ,, ,,
3,000 ,,	838 ,, ,, ,,

German Field Gun, 3·13 inches.

Bursting Velocity.

0 yards	1,525 feet per second

Austrian Field Gun, 3·01 inches.

Bursting Velocity.

0 yards	1,525 feet per second

German Mauser Service Automatic Rifle, 303 Mark VI.

Bursting Velocity.

0 yards	2,060 feet per second
500 ,,	1,281 ,, ,, ,,
700 ,,	1,103 ,, ,, ,,
1,000 ,,	961 ,, ,, ,,

Service S/05.

Bursting Velocity.

0 yards	2,820 feet per second
500 ,,	1,741 ,, ,, ,,
1,000 ,,	1,086 ,, ,, ,,

Mauser 7·63 mm. Automatic Pistol.

Muzzle velocity, 1,380 feet per second.

German Luger Automatic Pistol, 9 mm.

Muzzle velocity, 1,040 feet per second.

Thompson Sub-Machine Gun, 0·45 calibre.

Muzzle velocity, 1,030 feet per second.

We may divide these velocities into three categories: low velocity,, up to 600 feet per second, medium velocity, up to 1,200 feet per second, and high above this figure.

Let us turn now from the problem of protecting the soldier to the possibilities of solving it. I have been doing my best since the beginning of this war to point out that

FIG. 2.—Illustration of body armour the use of which by the U.S.A. Army is being considered. It is made of sections of chromium steel with an intervening layer. The area over the heart is thicker. It weighs 14 lb. and renders the wearer immune to a "Tommy" gun.

once having accepted the principle that it is worth while protecting the head against missiles of low and medium velocity by a steel helmet, there is no reason why we should not extend, in the case of the more highly mechanized units, this protection to other equally vital areas—such as the chest and the abdomen. At the end of the last war this would not have been a practical suggestion; in this war it is. Fig. 2 illustrates

a jerkin to cover the whole of the abdomen and chest which weighs only 14 lb. It will stand up to projectiles of low and medium velocity, in other words to shrapnel, hand grenades, revolvers, automatic pistols and to an, at present, indefinable percentage of fragments of shell and bomb. It will also resist a Tommy gun, but not rifle and machine gun fire much under a range of 1,000 yards. If, however, protection from high velocity missiles is required, we can achieve this by reducing the area protected to the front of the body and adding a couple of pounds to the weight. I cannot show you this heavier bodyguard as it is on its way from America.

Previously attempts were made to deal with these high velocities by the principle of deflection, that is to say, arranging inclined planes from which the bullet ricochets. This, while being far too cumbersome for body armour, is much employed in the protection of the pilot and the gunner in the Air Force.

So far we have only considered steel in protective armour. Nowadays, however, we have materials which have roughly the same tensile strength as aluminium and about half its weight. They can be moulded to any form and are of reasonable cost. I am convinced that there is scope for the use of such material in the protection of the fighting man. If desired, its stopping power can be increased by incorporating in it a fine wire mesh. Even if such protection were confined to backing the box-respirator with a plaque of compressed fibre it would save a certain number of the type of fatality which I described at the beginning of this paper.

Armed with all the knowledge I could acquire and fortified by the fact that the U.S.A. Army authorities were actually using the particular steel I have described I have spent the last month in and out of the War Office and the Air Ministry. I am glad to say that the latter is keenly interested in the question of protection, and is doing a great deal to protect its pilots and gunners. Unfortunately the War Office is entirely unresponsive and to the question, "What is the maximum weight of body armour to which you would give any consideration, and what are the minimum requirements with regard to protective power?" the answer received was: "We are not interested in the subject." It was mainly because of this that I have asked this meeting to be called. Either I am entirely wrong in my conclusions that more can be done to protect specialized units of the British Army or else I am entitled to the support of the profession in my efforts to induce the War Office to reconsider its decision. If I am wrong the German staff is also wrong. We are told that their shock troops are protected and in a letter recently received from America the writer states that before the war three efforts were made to induce a certain inventor to place his armour at the disposal of the German staff.

To summarize my conclusions:—

(1) Just as in the factories and in the mines there is close collaboration between the medical profession and the managers to protect workers against illness and injury, so should there be a far closer collaboration than at present exists between the surgeon treating wounds and the military, naval and air force authorities. Only by a close study of the type of injury from which a particular branch of the Service suffers can we evolve the necessary methods of preventing it. Let us take for example the medical observation that many airmen are coming down with superficial burns strictly limited to the hands, forearms, face and neck. If this is the case may it not be possible to protect these areas by means of asbestos emergency gauntlets and helmets to be put on rapidly when petrol fumes fill the cockpit and there is danger of fire.

(2) If anything is to be achieved along these lines the initiative must come from the medical profession. This is not only my opinion, but also that of the few sympathizers I have met in the War Office.

(3) One of the reasons why this subject of better protection is being completely ignored is that there is no single authority to deal with it. Since I have interested myself in the matter I have been inundated with correspondence from people who have failed to obtain any consideration of their suggestions, and have finally given up in despair. If this is to be remedied a single body competent to deal with the whole subject must be appointed. When I was recalled from France to be attached to the Ministry of Munitions at the end

of the last war, I was told that there were experts in armour working in conjunction with the French and Italian armies and that I must get in touch with them. If it was felt necessary to give special consideration to this subject in 1918, it is still more necessary in 1940.

Discussion.—Sir RICHARD CRUISE said that his work in connexion with this subject was limited to the protection of the eyes, and he was not prepared to say more than, very briefly, what he had done in that respect. In 1917 he produced a visor attachment to the steel helmet, and recommended it in a paper read to the annual congress of the Ophthalmological Society in that year. The purpose of this attachment was to eliminate preventable blindness. Figures which he brought forward in 1917 showed that from 50 to 70% of all war blindness was preventable. The majority of ocular injuries occurring in war were the result of small fragments entering the eye, the result of any form of explosive, bomb or grenade, with scattering of particles. Thus an injury which would have been negligible in any other part of the body was liable to be disastrous in its effect upon the eye. The definition of "preventable injury" must be more or less elastic, but he submitted that an injury could be described as such if caused by a missile which, in the case of the eyes, would have been stopped by a screen or visor.

With the help of the Research Department of an aviation company during the past few months he had invented a visor of great simplicity and effectiveness. This was moulded so as to fit the inner curvatures of the steel helmet, to which it was attached by rivets. It was, in his view, an essential portion of or complement to the steel helmet, and he would like to feel that in the future no helmets would be issued without the attachment of the visor.

One of the difficulties he had had to overcome in urging the claims of eye protection was the ingrained idea of the toughness of the eyeball. He had carried out tests of the visor by firing at it with a 12-bore shot-gun. He found from experiments with pigs' eyes that the unprotected eye could be completely destroyed at 40 paces. On the other hand, at 30 paces, with the visor, there was no penetration.

The principle of the desirability of ocular protection was accepted by the War Office in 1917. The primary desideratum for any form of body armour was that it should be efficient and should not interfere with the efficiency of the soldier. This visor was an integral part of the steel helmet. It was not a separate piece of equipment like goggles, which could easily be lost, and it was durable. It was capable also of being brought into instant effectiveness. While it would not stop a bullet at close range it would prevent small fragments of low kinetic energy from entering the eye; such fragments were a very large cause of blindness.

Sir HAROLD GILLIES said he hoped that as a result of the meeting a strong committee would be formed by the Society to ventilate this matter in such a way that the principle was adopted. With regard to protection of the face, Sir Richard Cruise's visor undoubtedly would help. One suggestion that might improve Mr. Walker's breast plate would be to have a flange on the point of the shoulder arranged in such a way as to protect the big vessels from a missile from the side.

The War Office should consider a type of windscreen which would afford extra protection to the motor driver or cyclist.

As regards protection from burning it was obvious that in all the Services the hands as well as the face were liable to be burnt; frequently the hands were held in front of the face the damage being greater on the back of the hands than on the palmar surface. The result was stiff joints if nothing worse, rendering the man useless for the rest of the war. If some gauntlet could be made of fire-resisting material—the ordinary leather glove afforded only a slight protection for a short time—it might prove of great value and should not interfere with the pilot, observer, or driver.

The PRESIDENT read a note from Major Underwood on the question of the kind of wounds most commonly seen during the present war. He stated that he was of the opinion that quite a number of the wounds were due to low-velocity or medium-velocity projectiles. The foreign bodies were in the majority of cases due to high explosives. He instanced the small size of the fragments as compared with those experienced in the last war.

Colonel MAX PAGE said he gathered that Mr. Walker thought armour should be worn only by specialized troops. He was not quite sure that the armour should not be on the vehicle instead of on the back. It was an important point of view that the

fighting man must not be hampered in any way, although he should be protected to the utmost extent.

He had been interested to hear of the remarkable forms of protective material which could now be obtained. If such material were added to the tank or vehicle in which the man was riding, or even to the motor ambulance, it would furnish a real protection in some respects.

He did not think that there was any evidence that the Germans were using armour for infantry in this war. The type of wound varied with the type of warfare, and in modern mechanized warfare it was remarkable that there was an increase in bullet wounds.

Surgeon Rear-Admiral GORDON-TAYLOR spoke sympathetically in favour of the protection advocated by Mr. Kenneth Walker and by Sir Richard Cruise.

Sir THOMAS DUNHILL wished to express his sympathetic support. The medical profession had done much in establishing preventive medicine for the whole population. Now they had a special opportunity of seeing the type of injuries wrought by rifle bullets, high explosives, and incendiary bombs. Without doubt many of these injuries could be prevented by light armour. The question seemed to be how to give soldiers this protection without impeding their mobility. With regard to the small size of shell fragments found in this war as compared with the last: in this war of rapid movement it is probable that a far higher proportion of the more seriously wounded were not collected, whereas the more lightly injured had a greater chance of getting away.

Though there was apparently no evidence to what extent, if at all, the Germans were protecting their men, he thought that information on the subject from all points of view should be carefully considered. Conclusions could then be put forward in such a fashion as to command consideration.

Mr. T. B. LAYTON opposed additions to the weight of equipment. Allenby put 70,000 men into Beersheba. Mr. Kenneth Walker's 14 lb. meant for these 400 tons or 40 ten-ton lorries. How many companies of the R.A.S.C. was this? How many shops of the R.A.O.C. did it mean? How much petrol? How many depots for it? When these figures were multiplied to the whole Army they would see the difficulty the medical authorities would have in getting the suggestion past the Q.M.G.

On the other hand he had been interested by the protection afforded the soldier in action by something in the pocket covering the vital area over the heart; if Mr. Kenneth Walker could produce something weighing 2 oz. which would cover this vulnerable area they might get it through. Two ounces was an important amount when discussing transport and equipment.

Colonel A. E. PORRITT referred to the absence of chest and abdominal cases seen in base hospitals, which had then to all intents and purposes become casualty clearing stations. Before they left France they had over 2,000 cases, and he did not believe that among them there were a dozen chest or abdominal wounds. This would seem to provide ample confirmatory evidence of the high mortality in this type of case, which would obviously be lessened in some degree by the use of body armour. He agreed with Colonel Max Page as to the enormous number of wounds which were due to missiles of low velocity, but pointed out the marked relative increase in through and through wounds (from machine and " tommy " guns) seen in the latter weeks of the campaign in France.

Mr. ASLETT BALDWIN said that a lighter apparatus than the 14 lb. one might suffice. He suggested that the matter be looked into by a Committee and recommendations sent to the Prime Minister. It required a man with war experience and a good drive in him, to get an important matter like this put through quickly.

Petrol tanks should be better protected, because numbers of men had been burnt by the petrol catching fire through the perforation of the tanks, and the men and planes lost.

Mr. JOHN BUNYAN said it seemed to him that protection by armour could be very much improved. He then suggested a method which would result in increased protection with less weight. He had been impressed by Sir Richard Cruise's visor, and he felt it might have a slight addition at the side and back to protect the head and neck.

Mr. OGIER WARD (communicated): With regard to his recent experiences in France, many casualties in the open came from air attack. In such cases the natural reaction of

the human being was to crouch; he had noted a great increase in wounds of the buttock and back and of the back of the neck. Mr. Ward recalled several cases of bad wounds caused by splinters of low velocity entering the neck. He also pointed out that the English helmet was greatly inferior in design to the German. It not only did not protect the temple region, but afforded no protection behind. He suggested that a curtain of chain mail be attached to the back of the "tin hat", coming down as far as the 7th cervical vertebra, rather like what was worn in the tropics dangling behind the topee to protect the neck from the sun.

Mr. Ward added some remarks on which he did not want any particular emphasis to be laid, to the effect that he had noticed that in the Tank Corps there were large numbers of badly comminuted fractures of the femur among the casualties, but very few wounds of the upper part of the body. That was just the sort of subject which needed study. Why should so many men of the Tank Corps suffer from fractured femurs? It might be that the missiles were so powerful that anything in the upper part of the body was fatal, or it might be that some alteration in the design of the tank might prevent these particular wounds which were so common.

Mr. E. D. D. DAVIS supported Mr. Kenneth Walker and Sir Richard Cruise. In the last war he was surgeon to a casualty clearing station which was a head centre, and he took a great interest in the "tin hat". Harvey Cushing, in a paper, reproduced some photographs of "tin hats" which were extensively damaged but the wearers received no more than scalp wounds without penetration of the skull. The British hat was as efficient as the German helmet. The French first used the helmet about May 1915, it weighed 22 oz. and could resist a projectile travelling at 400 ft. per second. The British went one better, their hat weighing 21 oz. and was able to resist a projectile travelling at 750 ft. per second. The German helmet was introduced in January 1916. It was 14 oz. heavier than the British hat, and this and its shape added very considerably to its discomfort. He was sure that the British hat was more comfortable and a greater protection from air attack and also when the soldier was in the prone position. He suggested that a surgeon and an officer who had experience of the front line should discuss possible improvements in headwear and other matters. The German helmet had the disadvantage of being more easily seen, and its contour was such that it was less able to deflect missiles.

Mr. MCADAM ECCLES asked whether the relation of the visor to the gas mask had been considered. Another point to be borne in mind was that warfare was probably going to be in the home country, and he thought that Mr. Walker was right when he said that they wanted real protection, even if it involved greater weight, because, after all, this extra equipment would not have to be carried very far, at any rate not carried by the men themselves.

Mr. KENNETH WALKER, in responding to the discussion, said that he did not think it necessary to reply to every speaker, but he would take up a few of the salient points. Colonel Max Page had not seen armour used by the Germans. That was a question on which he was trying to get information, but it was difficult. One war correspondent, Mr. Hodson, in Belgium, had referred to armour being worn by the enemy. To what extent were they using it?

He quite agreed with Admiral Gordon-Taylor that the sailor should not be encumbered by weight.

In answer to Mr. Layton he thought it would be possible to produce something weighing two ounces to cover the vital area over the heart.

Great stress had been laid on the subject of burns, and all possible methods of protection should be carefully considered. He was glad to hear Mr. Davis stand up for the British "tin hat", but he would not go into detail at this point as his present aim was to ensure that these matters should be seriously considered by the profession. With this view he had tentatively framed certain resolutions which would be proposed from the Chair.

The following resolutions were proposed by the President and carried unanimously:—

(1) That this representative meeting of the Royal Society of Medicine, after a full discussion of the question, is emphatically of the opinion that the physical protection of the members of the fighting forces can and should be improved by a closer collaboration between the medical profession and the appropriate technical experts of the Admiralty, War Office, and Air Ministry.

(2) That this meeting of the Royal Society of Medicine resolves that the Council of the Society be asked to consider the formation of a special committee to this end, according to By-law 21; furthermore, as the matter is, in the opinion of this meeting, one of extreme urgency and importance, it is hoped that the President may use his emergency powers and approach the Government with the offer of the Society's co-operation at the earliest possible date.

Section of Psychiatry

President—F. L. Golla, O.B.E., F.R.C.P.

[*April* 9, 1940]

The Action of Adrenaline in Anxiety

By Derek Richter, M.A., B.Sc., Ph.D.

The part played by adrenaline in the major emotions of anger and fear has been generally recognized since the classical work of Cannon, who obtained evidence of a liberation of adrenaline from the adrenals and showed that the main somatic accompaniments of anger and fear could be attributed to the action of adrenaline.

There are few to-day who take the extreme view of James and Lange in regarding the emotions as little more than our perception of these bodily changes, yet the somatic effects are an important component of emotion. In anxiety it is certainly the somatic symptoms of which the patients chiefly complain and this is important from a therapeutic point of view, since it is frequently possible to relieve the condition to a considerable extent merely by removing the physical symptoms (Misch, 1935).

Anxiety cases often show symptoms such as diarrhœa or sweating which are produced by a cholinergic mechanism, but generally the main symptoms are referable to the action of adrenaline. The relationship between the effects of adrenaline and the anxiety state is further emphasized by the emotive action of adrenaline.

Patients frequently show emotional symptoms after a small dose of adrenaline. Generally it causes only a vague feeling of apprehension or anxiety, but often it produces a marked emotional upset: the patient may burst into tears and experience a profound emotional disturbance. The emotional response to adrenaline is absent in chronic schizophrenics (Dynes and Tod, 1940). Maranon (1924) found that it is generally slight in the most normal individuals and his work suggests that the response is particularly exaggerated in anxiety neurotics.

The observed sensitivity to adrenaline may depend on (*a*) the rate of destruction of adrenaline in the body, (*b*) the physiological conditions, involving such factors as pH, thyroprotein level and calcium level in the tissues, and (*c*) the mental condition of the patient.

Before we can get very far with this problem it is necessary to know more about the basic physiological and biochemical factors which control the action of adrenaline and particularly how it is inactivated in the body. We know that the activity of acetyl choline, which is liberated in the parasympathetic division, is controlled by the enzyme choline esterase which destroys it. It may then be asked if there is a corresponding enzyme which inactivates adrenaline liberated in the post-ganglionic sympathetic division.

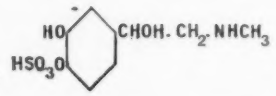
Until recently, nothing was known of the way in which adrenaline is inactivated in the body and this has held up research on the sympathetic nervous system to a considerable extent, since in nearly all experiments in which the effects of adrenaline are measured the rate of inactivation of adrenaline comes in as an unknown and possibly variable factor.

The effects of a subcutaneous adrenaline injection may last for an hour or more owing to the local vasoconstriction and slow rate of absorption, but adrenaline is rapidly removed from the circulation since the effects of an intravenous injection are brief and last for only a few minutes.

It has frequently been assumed that adrenaline is oxidized in the body and it has been suggested that the oxidation might be effected by the amine oxidase, an enzyme which is mainly responsible for the detoxication of amines in the body (Richter, 1938). This view was supported by Gaddum (1939) who put forward a theory of the action of ephedrine which is based on it; but recent work has shown that the rate of inactivation of

adrenaline in the body is too great to be accounted for by the amine oxidase (Richter and Tingey, 1939) so that we must look for some other enzyme.

The problem of how adrenaline is inactivated in the body has now been studied in a new way by taking large doses of adrenaline by mouth and searching for reaction products of adrenaline in the urine. It was found that after taking adrenaline a substance appears in the urine which has the properties of an adrenaline ester (Richter, 1940). The amount of this adrenaline ester found in the urine is necessarily small, since only small doses of adrenaline can be given, and it has not yet been isolated in the pure state, but the chemical work has advanced sufficiently to show that it is probably the sulphate ester or "ethereal sulphate" in which adrenaline has been conjugated with sulphate on one of the phenolic hydroxyl groups. About 70% of the amount of adrenaline administered was found in this form in the urine.



This suggests that the chief method by which adrenaline is inactivated under physiological conditions is by conjugation and the inactivating enzyme is the "sulphosynthase" or system responsible for the synthesis of sulphate esters. There is further evidence which supports this view. It might be expected that adrenaline, which is a phenol, would also be inactivated in the same way as other phenols, which are known to be mainly detoxicated by conjugation. Animal experiments have shown that the liver is particularly effective in inactivating adrenaline since the effects of adrenaline are prolonged and intensified by hepatectomy; the liver is also the chief site in which the detoxication of phenols by conjugation occurs.

Strong evidence of the function of choline esterase was afforded by the discovery of the anti-choline esterases, which prolong the effects of acetyl choline by competing with it for the enzyme and so preventing its destruction.

If adrenaline is inactivated by the "sulphosynthase" we might expect that other phenols would act in a manner analogous to the anti-choline esterases by competing for the enzyme and so prolonging the effects of adrenaline. This has been tested and Bacq (1936) found in some very striking experiments that polyphenols injected *in vivo* do, in fact, augment and prolong the effects of adrenaline. After injection of polyphenols the animals appeared hypersensitive to adrenaline or to the effects of stimulating the sympathetic nerves.

It would therefore appear probable that the system in the sympathetic division corresponding to choline esterase is the "sulphosynthase" and the polyphenols correspond in their action to the anti-choline esterases.

I have mentioned this work because a deficiency in the system inactivating adrenaline is a factor that might well play a part in certain types of anxiety and this is a possibility which cannot yet be excluded. These experiments, in showing that adrenaline is eliminated in a form that can be estimated in the urine, may also suggest other lines of investigation on the problem of anxiety.

Coming now to the physiological factors which affect the sensitivity to adrenaline, it is known that the intensity of the reaction to adrenaline runs parallel with the thyroprotein level and is increased in acidemia and after the administration of calcium. There are also many other factors such as the adrenal cortical hormone and sex hormones which have been stated to affect the sensitivity to adrenaline. In the present study I am particularly concerned with the emotional response to adrenaline, and Maranon, who investigated the point very thoroughly, established that the physical and emotional reactions to adrenaline are not directly related. It is true that an intense physical and emotional reaction frequently go together, but on the other hand there may be an intense physical reaction without any corresponding emotion. The emotion is not therefore directly determined by the physical response.

Before passing on to consider the mental factors there is one further biochemical process by which adrenaline might conceivably affect the emotional state.

Adrenaline causes an initial rise which is frequently followed by a secondary prolonged fall in the blood sugar, the fall being due to the diminished glycogen reserves and increased liberation of insulin. It is well known that a fall in the blood sugar is associated with nervous symptoms related to anxiety. This is shown for example in the anxiety which may be one of the first effects of an insulin injection. Many apparently normal individuals, and particularly "nervous" children, experience a mood of anxious depression in between meals and this is intensified by emotional excitement. The observation that this condition can frequently be relieved by administering glucose suggests that the fall in the blood sugar may be the main factor in determining the type of anxiety. That it is most commonly found in children may be attributed to their relatively high metabolic rate.

Until recently it was believed that adrenaline causes a breakdown of glycogen in the liver by activating the liver amylase, but it has now been shown that adrenaline acts on the phosphorylating system and increases the rate of phosphorylation of glycogen (Lee and Richter, 1940). The immediate hyperglycæmia causes a secondary liberation of insulin from the pancreas which may result in a marked hypoglycæmia. This effect of adrenaline on the glycogen reserves and blood sugar may possibly be a significant factor in the type of anxiety which responds to glucose and which is commonly found in "nervous" children; but this is still only a speculation and further research is needed to confirm it.

Returning now to the consideration of the direct emotional action of adrenaline, previous investigators have generally observed the effects after administering adrenaline by injection, but an injection which causes obvious physical effects may in itself be sufficient to cause anxiety in some subjects. I have found it an advantage to introduce the adrenaline electrically through the skin. The application of two small electrodes causes little discomfort or apprehension and the subject need not know that any drug is being put into him.

Maranon concluded that subjects may respond to adrenaline either by (*a*) a vague emotional sensation in which the somatic elements of emotion are perceived "en froid" or by (*b*) an outburst of true emotion in which the somatic and psychic elements are both present. This classification into two categories may be useful in drawing attention to the fact that the emotional response is different in different individuals, but in my experience these two types of response are not clearly defined but merge imperceptibly into each other.

The most normal subjects generally experience a feeling of apprehension which is well expressed by one subject who said: "I feel weak-kneed, as if I was just up for an exam!" This sensation is not a true emotion, but might be described as emotion with insight, for the subjects know that they have no real cause for emotion.

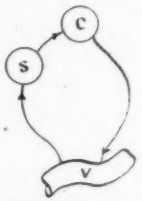
The simplest interpretation of the causation of true emotion by adrenaline is that the subject becomes conscious of the cœnæsthetic impulses arising as a result of the somatic disturbance and begins to think of previous emotional experiences in which he has felt a similar sensation and which, by repetition, may have become associated with this particular bodily sensation. The subject may, for example, think about his income tax, which has been causing him some anxiety. The consciousness becomes focused on subjects with a similar emotional content and the patient may begin to rationalize and find in these subjects sufficient reason for his feeling of apprehension.

If, as often occurs in anxiety neurotics, the mind contains some pattern that is highly charged with emotion (corresponding perhaps to the Freudian "complex"), the cœnæsthetic impulses produced by adrenaline may act as a form of suggestion and may give rise to an emotional discharge. This emotional discharge may in itself be sufficient to cause a further release of adrenaline through the action of the sympathetic nervous system; the original cœnæsthetic impulses are thereby increased and a vicious circle may result. The emotional response to adrenaline is most simply interpreted in terms of a "cœnæsthetic cycle" of this kind, in which there is a mutual interaction between a cortical pattern and a visceral organ so that each may increase the degree of excitation of the other (*see* illustration, p. 48).

The way in which the cœnæsthetic impulses arising from a visceral disturbance may cause the excitation of an emotionally charged cortical pattern (path VSC) is illustrated by the anxiety dreams, which may occur as a result of indigestion, a process which is

particularly marked in anxiety neurotics. The production of visceral changes by an emotional discharge (path CV) is well established.

The emotional response to adrenaline does not always take the form of anxiety, but depends on the type of emotional pattern which is associated in the subject with sensations produced by adrenaline. Maranon described a patient who expressed his sensations



Cœnæsthetic cycle.
V = viscera. S = sensory perception. C = cortical pattern.

after an adrenaline injection as being as if he was "expecting a great joy". This was illustrated similarly by a case I observed of a woman of 33 who was liable to attacks of anxious vomiting. She held an influential position as a civil servant and for many years she had felt sick and vomited before any important interview or before giving a lecture about which she felt anxious. She gave a clear emotional response to adrenaline, but it was not her usual anxious vomiting. Following an adrenaline injection she flew into a temper and became aggressive in her manner. Afterwards she tried at first to rationalize her behaviour, but finally said: "I just felt terribly angry—I can't think why!" One subject who was used to taking adrenaline as a remedy for asthma stated that adrenaline gave him "a feeling of confidence", which is the reverse of anxiety: this may be attributed to his associating the sensations produced by adrenaline with the relief of his asthmatic symptoms.

Lindemann and Finesinger (1938) have shown that the property of precipitating an anxiety attack is not specific for adrenaline, but attacks can sometimes be induced by mecolyl. It seems likely that a "cœnæsthetic cycle" is again responsible, but in this case there is an emotionally charged pattern associated with impulses coming from the parasympathetic division.

A cyclical mechanism of this type is well known to operate in normal sex behaviour. Here again an emotionally charged cortical pattern interacts with the impulses coming from a visceral organ and stimulation of either may increase the degree of excitation of the other. The cycle can in this case be started by direct stimulation of the organs, by suggestion or chemically by yohimbine and the aphrodisiacs, which act in a way which may be compared with the effect of adrenaline in inducing an attack of anxiety.

In certain types of anxiety state the various biochemical factors I have discussed may come in as a part of the picture, but the observed hypersensitivity of anxiety neurotics to adrenaline is most simply explained in terms of a cyclical mechanism which is conditioned by their having an emotionally charged cortical pattern which is excited by the impulses coming from a visceral or peripheral organ so that each tends to increase the degree of excitation of the other.

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Section for the Study of Disease in Children

President—Surgeon Rear-Admiral CECIL P. G. WAKELEY

[*April* 26, 1940]

DISCUSSION ON INTRATHORACIC TUBERCULOSIS IN CHILDHOOD

Dr. N. B. Capon: From the vast literature which has grown about the subject of intrathoracic tuberculosis in childhood the facts tabulated below have been proved beyond dispute :—

(1) Intrathoracic tuberculous infection is common in childhood and infancy; it is usually contracted from adults who are in immediate and fairly prolonged contact with the child.

(2) In many cases the early (primary) infection causes only slight ill-health and may be difficult to diagnose with certainty.

(3) Many infants recover satisfactorily from the primary infection, especially if they are removed from infection at an early stage; but when the disease progresses until it is recognizable by ordinary clinical methods the outlook is serious, especially in infants under two years.

(4) The most valuable special methods of examination are: (*a*) The search for *B. tuberculosis* in material obtained from the throat or from the stomach. (*b*) Testing for sensitivity to tuberculo-proteins. The reaction is specific and delicate; fallacies may arise if technique is not perfect. (*c*) Radiography.

Immunity (specific and non-specific), intrathoracic allergic reactions and "re-infection" tuberculosis are not included here as much of our knowledge is still largely hypothetical.

The correlation of clinical and pathological findings will be still closer when we give greater weight to the varying characteristics of pathological change at different age-periods. A well-recognized example of this principle is the reaction of lymphatic tissues to infection at different ages. Such a conception may well provide a truer explanation of, say, the differences which are found between primary tuberculosis in childhood and in early adult life than the suggestion that they depend upon the operation of such factors as allergy, susceptibility, and immunity; though their mode of action too may eventually be understood and may indeed be intimately linked with the pathological changes.

In the examination of a private patient who is suspected of tuberculous infection, it is wise to explain to the child's relatives the difference between tuberculous infection and tuberculous disease before the investigations are undertaken; and in some cases, where the relatives are obviously neurotic, it may be necessary to be guided entirely by the results of ordinary clinical examination; for the stigma of suspected tuberculosis is harmful to a child's progress under these special circumstances. The obvious danger of this course is that further contact with an infectious adult might continue.

Two main clinical difficulties have to be faced :—

(1) To decide on the most suitable treatment for the child with extensive intrathoracic tuberculosis whose general health, as judged by colour, state of nutrition, and playfulness, is good. These cases are not uncommon in hospital practice.

(2) The assessment, especially from the prognostic point of view, of pulmonary changes which at their beginning are non-tuberculous, though they are undoubtedly secondary to tuberculosis: e.g. collapse of a lobe, and compensatory emphysema.

The prevention of intrathoracic tuberculosis in childhood is still the most perplexing aspect of this subject. The relationship between the child and those adults who are responsible for his care is so close that infection is liable to spread even in good surroundings. Increased use of preventive inoculation should help; but "tuberculo-phobia" should not be encouraged by lectures and writings intended to educate the lay public.

Dr. Reginald Lightwood: In the treatment of primary tuberculosis some authorities advocate a careful and prolonged regime, and yet others believe that healing takes place equally without it. Obviously this important question should be settled.

Because minimal infections are widespread among urban children, a distinction is commonly drawn between this *tuberculosis in its minimal degree* and *manifest tuberculosis*. Minimal infection has been referred to as a *tuberculous process*, while manifest tuberculosis is a condition of disease. Conscientious case-finding tells us that many children at the time of their first infection pass through a period of disturbed health which is not recognized as symptomatic of tuberculosis unless appropriate investigations are applied. Probably all will agree that a child in good general condition, in the absence of radiological change or any disturbance of health, not even a rise of temperature, is in no need of treatment. But what of those cases in whom the first infection can be recognized at its inception by modern methods of diagnosis?

There are many who think that the treatment of first infection tuberculosis can be overdone, especially as the disease in childhood is usually benign. Some workers have gone further by saying that primary tuberculosis need not be treated in hospital because recovery is the rule (Stewart, 1932). They would prefer to spend the money on other measures of tuberculosis control (Myers, Harrington, Stewart, Wulff, 1935).

Myers and his colleagues were early in their enthusiasm to organize the diagnosis and treatment of first infection tuberculosis, but in 1935 a follow-up of the results obtained at the Lymanhurst Health Centre in Minnesota brought about a unanimous change of policy. Whether the child went to a sanatorium, special school or remained at home, they could trace no difference in the long run. It seemed all first infections were so benign that no special treatment was necessary, and that the patients who ultimately did badly were all of the "re-infection type". This report from Lymanhurst states that 20% of tuberculin-positive children ultimately developed re-infection type of pulmonary tuberculosis (10% by 21 years of age). They believed that treatment in the primary phase could not prevent this.

Stewart (1932) indeed had previously written that unless the patient had radiographically demonstrable recent changes in the lung parenchyma, he had nothing to fear from the primary infection, and, morever, that institutional treatment of primary tuberculosis, especially in infants, might be more dangerous than the disease, a most important practical point, but perhaps more an argument for the provision of suitable institutions with better facilities for nursing, open-air, bed-spacing and isolation, than one against the value of proper sanatorium treatment. A general hospital is not a safe place for the treatment of primary tuberculosis unless separate and special accommodation can be arranged.

The arguments against institutional treatment of primary tuberculosis have been given prominence and there is danger less the case in favour of it, in suitable and selected patients, should go by default. Clinical workers have too easily assumed that more or less prolonged special treatment, often in hospital, is necessary. There is a disappointing lack of critical study concerning the immediate and distant results of treatment in sanatorium or preventorium. For this reason the early investigations of Borrel (1920) and the more recent work of Hawes, Wood and King (1934) are the more welcome.

Borrel deals with the problem of first infection tuberculosis in adults and the reaction of coloured troops who previously had had no contact with the disease. When the Senegalese troops were first brought to France, tuberculosis was almost unknown amongst them and only 2% or 3% reacted positively with tuberculin: these were usually found to have lived in North African towns. In the first year of their sojourn in France tuberculosis began to appear in the battalions, and later its incidence rose steeply through contact infection in barracks, until prophylactic measures were instituted. The disease was of the first infection pulmonary type and comparable to primary tuberculosis in childhood. Many cases showed a rapidly progressive course and miliary tuberculosis was common. After a system of inspection and early diagnosis had been instituted, Borrel found that when the affected soldiers were taken into hospital and given rest, fresh air and a generous diet with cod-liver oil, they often recovered in two or three months (apparently about 50%). Whereas, if they remained on military duty doing intensely hard work, their condition deteriorated and they entered the category "définitivement perdu". Borrel's report does not give statistically satisfactory information, but his

material comprised large numbers of soldiers with extensive post-mortem records to check his observations ; his main conclusion bears the stamp of probability.

Hawes and his colleagues (1934, 1935) studied a smaller body of material and compared 704 children who had been under treatment for first infection tuberculosis at Prendergast Preventorium with an equal number showing a positive tuberculin reaction who had not had preventorium treatment.

ANALYSIS OF RESULTS FROM THE PRENDERGAST PREVENTORIUM, BOSTON TUBERCULOSIS ASSOCIATION.

A Study of Ten Years' Work.

Follow-up of 704 children treated for primary pulmonary tuberculosis in the preventorium.		Follow-up of 704 untreated children with positive tuberculin tests.	
Tertiary tuberculosis	3	Tertiary pulmonary tuberculosis	40
Deaths	1	Deaths	10

In assessing the above results it should be stated that the work of the preventorium did not end when the children went home. Possibly half the benefit obtained might be attributed to the educational activities aimed at improving general hygiene, and the provision of medical and social supervision afterwards.

Wallgren (1939) recommends prolonged treatment in the cases which he calls "fresh primary tuberculosis". He says that among 528 children admitted with erythema nodosum and treated for primary tuberculosis, only three developed tuberculous meningitis, while in the same period he admitted to hospital 23 cases of tuberculous meningitis who had a preceding history of erythema nodosum, of whom only three had been appropriately treated for primary tuberculosis. Wallgren finds that pleurisy cannot be prevented by treatment, and that it appears not infrequently in patients undergoing strict treatment.

In England, Scandinavia and elsewhere most pædiatricians favour careful and lengthy treatment of primary tuberculosis, either domiciliary or institutional. Experience shows that there is definite evidence of the benefit thus obtainable in the early and active phase of primary tuberculosis and this evidence should be presented as well as the late results of follow-up studies. The indications for hospital treatment are more often social or psychological than medical. The home conditions sometimes make suitable treatment impossible because of economic strain. When one or other parent has pulmonary tuberculosis there is the danger of the infected child remaining in contact with the source of infection, and there is the further difficulty of keeping a child of 2 or 3 years old in bed, particularly in a small home when the mother has no one to help her.

The nature, duration and place of treatment must be determined separately for each patient. The desiderata are rest, nourishment, avoidance of infectious disease, and medical supervision. Healing is favoured by obtaining rest of the diseased part; rest in bed with the minimum of bodily and pulmonary activity is the most important measure during the acute stage. We may usefully compare the treatment to that given to children recovering from juvenile rheumatism; in the convalescent tuberculous child radiography occupies the same degree of importance as cardiac examination in the rheumatic child. To obtain full benefit from treatment the earliest possible diagnosis is necessary. During the early acute phase of the infection, the child often looks debilitated, suffers fatigue and more or less fever, and the sedimentation rate is raised ; the weight may be stationary or falling. Soon after treatment is begun the clinician may note clear evidence of improvement in the general health. Thus it is quite common to see a child with epituberculosis and raised sedimentation rate begin to put on weight soon after he is put to rest. But until the sedimentation rate has fallen to normal and remains there after exercise, it is too soon for the period of bed-rest to cease. Broadly speaking, this period is determined by the sedimentation rate which is to be regarded in the way that fever is in more acute infections. It is a more sensitive method of examination than taking the temperature. Nevertheless, it must not be assumed that the sedimentation rate runs either parallel with the temperature or tells us when the disease is no longer in an acute phase. Radiology shows that pulmonary infiltrations remain in evidence sometimes for months after the sedimentation rate has returned to normal, and occasionally the sedimentation rate remains high without any explanation of the cause being evident by radiography or in the general condition of the patient (Wallgren, 1939).

When the child has passed through the more acute stage of the infection, a suitable

amount of rest during the day must still be enforced, either out of doors or in a room with the window open.

The diet should be rich in protective foods, and cod-liver oil or a vitamin preparation is usually prescribed. The common practice of giving a calcium salt to encourage calcification in the healing lesions has only a little support from experimental evidence.

In this country we do not practise artificial pneumothorax in the treatment of primary tuberculosis, and Wallgren states that he has never induced it in a patient with this condition. He has never had occasion to regret this policy for the infiltrations heal up notwithstanding, and he is critical of all measures which cannot be regarded as absolutely necessary for this benign type of disease. On the other hand Armand-Delille practises artificial pneumothorax and his indication is the finding of tubercle bacilli by any method; by artificial pneumothorax he obtains very satisfactory results and the children become free of tubercle bacilli.

The difficulty of providing institutional treatment.—In England there is a shortage of sanatorium accommodation for children suffering from primary tuberculosis, especially for those under the age of 2 years. There are practical reasons for considering the cases of the infants separately. In children over two years the immediate risk is small, nursing care is not difficult, and provided they are not coughing, they may be treated as non-infectious. Yet it is practically impossible for a hospital almoner to get a child accepted for a convalescent home even if the only sign of tuberculosis is a positive tuberculin test; and the accommodation for the child notified as suffering from tuberculosis is rather limited, indeed in some cases, by the time a vacancy has been secured, the primary tuberculosis has so far healed that it has not been necessary for the child to go.

There is even less accommodation of a suitable type for infants under 2 years, at which time a large majority of the deaths occur, so that institutional care is most likely to be required. The following figures show the approximate fatality rate at different ages.

EARLY PROGNOSIS OF PRIMARY TUBERCULOSIS IN RELATION TO AGE: TREATED CASES (WALLGREN).

	Age-groups in years				Total
	0-1	1-3	3-7	7-16	All ages to 16
No. of children	39	64	225	125	453
Mortality rate %	35·9	15·6	4·4	0·8	7·7

Moreover, a severe and progressive type of disease which leads to cavitation is a characteristic consequence of the primary tuberculosis of infancy. Such patients are infectious and must be isolated. Infants treated in hospital run a risk of acquiring cross infections. The tuberculous infant needs in-patient treatment often of many months duration in a special ward provided with cubicles open to air and sun and where skilled infant nursing is available.

At the Hospital for Sick Children, Great Ormond Street, difficulty in securing proper accommodation for patients suffering from primary tuberculosis and the frequent long delay before removal to a sanatorium prevents the important early treatment. Such patients are sent to the Country Branch Hospital at Tadworth though the accommodation there is insufficient. The following details derived from the answers to a questionnaire, show how small is the accommodation for children under 2 years provided by the tuberculosis authorities, and the position is not much better for children over the age of infancy.

ACCOMMODATION AVAILABLE FOR BENIGN TUBERCULOSIS OF THE CHEST FOR CHILDREN UNDER TWO YEARS IN ENGLISH COUNTIES.

No accommodation 23		
Some accommodation 7		
Cornwall	Limited	No surplus
Essex	Yes	
Gloucestershire	32 beds	Very little surplus
L.C.C.	Yes	No surplus
Southampton C.B.	Yes	
Staffordshire	60 beds	Also serves Wolverhampton and Dudley
City of York	24 beds	Also serves East Riding
Surrey and Northumberland	No accommodation but are able to arrange in institutions not under tuberculosis authority.	

Thus we see that of the tuberculosis authorities who answered the inquiry less than one third are able to offer suitable accommodation for these infants and it follows that most tuberculous infants must be treated in a voluntary hospital, public institution or at home and the children's hospitals are forced to accommodate tuberculous cases for long periods.

Summary

Though statistical evidence in the form of follow-up studies is not sufficient to prove the point, it is probable that general treatment of primary tuberculosis in its early stage is justified, and the majority of clinicians support this view. Treatment in hospital is indicated more for social and economic than medical reasons. The child with primary tuberculosis is best treated at home or boarded out under good hygienic conditions, otherwise hospital accommodation must be provided, and this raises difficulties, particularly in infants. The tuberculosis authorities should pool their resources, and by joint action provide special accommodation for infants and children, in co-operation with the children's hospitals.

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Dr. Burton Wood demonstrated the special importance of radiology in the differentiation of the various forms of intrathoracic tuberculosis which may develop from the primary infection. Though post-mortem examination is seldom possible these developments may be studied by means of serial skiagrams in which the deposit of calcium often explains the nature of lesions which were doubtful at an earlier stage. The lateral views are specially important as they avoid the superimposing of shadows occurring in lobes which overlap in the antero-posterior position. Tomography makes a study of the hilar region more exact. The bronchoscope allows direct inspection in those cases in which gland tuberculosis is followed by bronchial ulceration and enables this complication to be correlated with the appearances seen in X-ray pictures. The tragic but impressive demonstration of the results following the ingestion of a known dose of living virus at Lübeck cleared up many difficulties. The demonstration of slides from X-rays showed the various forms of primary focus, of primary pneumonia, of "epituberculous" conditions and of the disseminated forms of pulmonary diseases, including the bronchopneumonic form and the acute and benign miliary forms.

Dr. G. Gregory Kayne: It is now recognized that examination of contacts is of great value in discovering active tuberculosis among people who would otherwise not consult a medical practitioner till weeks or months later, but there is still much disagreement on the value of such examinations in children. Those who do not think child contact examinations worth while usually believe that (1) pulmonary tuberculosis is rare in children, (2) accurate diagnosis is difficult and uncertain, (3) the discovery of such cases is not worth while since nearly all these children get well anyhow, or indeed do not feel at all ill, and (4) finally no treatment is known which will benefit children who are not likely to get well.

Those who consider that pulmonary tuberculosis is rare in children must think of the disease in terms of phthisis in adults. If so, they are right. But an active pulmonary lesion cannot be rare in childhood, in towns at all events, since at least three-quarters of the population are infected before reaching adolescence, and since even in this country of tuberculous cattle and unboiled milk, at least three-quarters of primary infections occur in the lung. Unfortunately the glandular component of the primary complex tends to divert attention from the primary pulmonary lesion—hence perhaps our discussion to-day on *intrathoracic* rather than on *pulmonary* tuberculosis in childhood. Moreover, because

most primary infections heal with little disturbance to the child, too little account is taken of the fact that in an appreciable percentage the outcome is by no means favourable. Some children die of generalized tuberculosis or tuberculous meningitis and some of bronchopneumonia following progression of the lung focus or rupture of a gland into a bronchus, and others suffer from long periods of ill-health due to perifocal inflammations (or epituberculosis), chronic disseminations or metastatic lesions in bones, joints, or elsewhere. In 1938, in England and Wales, one-tenth of all deaths in children aged 1 to 14 years were actually registered as due to tuberculosis, and this is probably an underestimate. In the individual child primarily infected we cannot prophesy the outlook, hence our endeavour must be to discover as many children as possible when in the active stage of the primary infection. The field is much narrowed when dealing with home-contacts, that is, children intimately exposed to massive infection.

Since July 1938, when I took over my district in Middlesex, 410 contact children under 15 were investigated by a routine described below. Forty-one (10%) were diagnosed as suffering from active primary or post-primary tuberculosis. The following table gives the age distribution :—

TABLE I

Age	Number investigated	Diagnosed tuberculous	
		Number	Per cent.
0—	18	2	11
1—	28	5	18
2—4	114	22	19
5—9	136	7	5
10—14	114	5	4
All ages	410	41	10

Only one of these children, a girl aged 14, was found to have pulmonary tuberculosis of the adult type. One child, aged 5, developed a tuberculous ankle soon after admission to sanatorium. Two children, brother and sister, were tuberculin-negative when first seen; six months later they were found to be tuberculin-positive and to have an active primary infection. Two children, aged 1 and 4 respectively, died of tuberculous meningitis in hospital within one month of being diagnosed as suffering from active primary tuberculosis and before admission to sanatorium.

These figures refer, of course, only to children in contact with active tuberculosis who attended the dispensaries as a result of the efforts of the dispensaries' staff and do not include children sent by doctors or brought by parents on their own initiative.

The fruitful search among the younger children as compared with those over 5 must be stressed (*see* Table I.) Indeed this might be expected. We need only refer to the tuberculosis death-rate per person of the same age (Table II). The failure of some tuberculosis physicians to find child contact examinations worth while may be due to the relatively few infants and young children investigated.

TABLE II

1938 : ENGLAND & WALES : TUBERCULOSIS MORTALITY PER 100,000 PERSONS OF SAME AGE.

Age	Tuberculosis mortality
0—	63
1—	73
2—4	36
5—14	16
0—4	49
5—14	16

In the diagnosis, such criteria as "pink and white complexion" and "long, sweeping, black eye-lashes" play little role. The steps are simple and clear, and there are no short cuts. Nevertheless the clinical diagnosis may be difficult and occasionally impossible. Physical examination is useless except in detecting non-tuberculous lung conditions. Radiological examination alone may be misleading since most of the X-ray appearances of tuberculosis, particularly enlarged hilar shadows, may be mimicked by non-tuberculous conditions. Routine skiagrams cause needless expense. The tuberculin test, indicating infection, is an effective sieve, and should therefore be carried out first : tuberculin-

positive children should be X-rayed. Since it is a negative and not a positive tuberculin test that is significant, the test must be complete. The recently introduced modification of the percutaneous test, the Vollmer patch test, though a convenient preliminary procedure when only one or two children are investigated at one session, does not exclude tuberculous infection with certainty, and should be followed by the intradermal test with PPD Second Strength or O.T. 1 : 100. In an infant even a positive tuberculin test is highly significant, for it indicates a primary infection almost certainly still active. After contact has been broken due allowance must be made for the ante-allergic period by re-testing until two months have elapsed.

The routine of preliminary complete tuberculin testing followed by an antero-posterior skiagram of tuberculin-positive children, and a routine lateral film in the younger age-groups, has been carried out on all child contacts from my district seen at the dispensaries since July 1938. The necessary attendances were good and the intradermal injection has not been refused by the parents in a single instance. The skiagrams obtained may be classified into several groups. The obvious calcified primary complexes in a symptomless child may be taken to exclude active tuberculosis. Skiagrams showing a circumscribed soft shadow in the lung field with an enlarged hilar shadow, or the characteristic bipolar shadow, show an active primary complex. Neither appearance is common, and the pulmonary focus may be very small or so situated that by itself it would not show up in a skiagram. Fortunately a periodical infiltration is often present, simplifying interpretation provided that a skiagram is taken two or three weeks later to exclude non-tuberculous and much more transient infiltrations. Occasionally we meet the miliary picture, with or without pleural involvement. A pleural effusion only may be visible in the skiagram. The interpretation of hilar shadows is often difficult. Here lateral skiagrams may be of great assistance as well as a knowledge of the anatomy of the bronchial glands, so ably worked out years ago by St. Engel. The routine sedimentation rate test in suspected children has been introduced too recently in my own work to quote results or conclusions. A normal figure does not exclude activity, and other possible causes must be excluded for a raised rate. Continental workers have found the examination of the gastric contents for tubercle bacilli of much help. This would presumably be carried out while the child was under observation in hospital, where temperature records can also be kept, but I have seen the gastric contents obtained routinely without apparent difficulty in out-patients in Sayé's dispensary in Barcelona. It is a good rule not to label a child with vaguely enlarged hilar shadows as tuberculous in the absence of symptoms.

Among my own 41 contact children diagnosed as tuberculous either in the dispensaries or after observation in institution, no less than 20 showed radiological pictures of perifocal infiltrations. In 15, there was only enlargement of the hilar shadows in the antero-posterior and lateral skiagrams or in the lateral film alone. In two of these children the diagnosis was subsequently in doubt at the Harefield Sanatorium to which they were admitted. Confirmation of the diagnosis ultimately rests on the appearance of calcification in the situation of the hilar shadows.

Even thorough investigation will miss most of the children we wish to discover. Unless the contacts are examined early in the course of the primary infecting case and the infants and young children are included, those for whom the outlook is poor will have already passed on to hospital with generalized tuberculosis or tuberculous broncho-pneumonia. The best results in child contact examinations are obtained when the supervision of the children with periodic tuberculin testing is begun *before* they have become infected.

Although most children will get well if nothing whatever is done about active tuberculous infection, we cannot indicate those in whom the infection will be fatal. Even those who get well must pass through a period of some months when their resistance is lowered to other infections. We do not know to what extent environmental conditions and food may influence the permanent healing of foci. But placing such children at rest and in a good hygienic environment will at any rate effectively increase the resistance of those on the borderline. Treatment on these lines is therefore indicated for all children with an active primary or post-primary lesion until the lesions have healed.

(Series of skiagrams illustrating (1) the findings in three or more members of the same family (four families) and (2) various phases of primary pulmonary tuberculosis in childhood, were demonstrated.)

Genital Dysplasia.—A. J. WALKER, M.B. (by permission of Dr. DONALD PATERSON).

J. T., aged 2 years, admitted to Westminster Hospital for determination of sex. Since birth this has been doubtful because of the anomalous development of the external genitalia.

History.—Second child; full time; normal labour. Birth-weight 7¾ lb. Breast fed for three months. No serious illnesses except for a severe attack of *B. coli* pyelitis one year ago. Mental and physical development appear normal. She commenced walking when 14 months old.

Family history.—Parents are fit and not related. Patient's elder brother, aged 5 years, is fit.

Condition on admission.—Weight 22½ lb. Appearance normal except for the genital abnormalities. There was no excessive fat and the complexion was normal. It was impossible to tell by inspection what the sex was since the clitoris was enlarged to about 1 in. long and about ½ in. in diameter, with a well-defined glans. The external labia were slightly pigmented and wrinkled like scrotal skin and there were some well-developed pubic hairs. Hb. 100%; R.B.C. 5,300,000. Skiagram of pituitary fossa normal.

A laparotomy was performed by Mr. McNab and two small spindle-shaped ovaries and uterine tubes and a small uterus were discovered. There seemed to be no vagina. There was no enlargement in the region of the suprarenals. The external sinus below the clitoris ends blindly and it is impossible to pass a probe into the bladder.

Severe Gastro-enteritis: Recovery after Mastoidectomy.—J. B. ATKINS, B.M. (by permission of Dr. DONALD PATERSON).

Brian W., aged 5 months.

25.3.40: Admitted in dehydrated condition necessitating intravenous saline therapy. Pyrexial.

29.3.40: Both drums incised in spite of normal appearance. No pus obtained.

Schilling index 0·56 (normal 0·07). (Mature forms 25·0%, "stab" forms 14·0%.)

30.3.40: Bilateral mastoidectomy by Mr. Crooks. Both mastoids filled with pus, giving pure growth of *Staphylococcus aureus* on culture. No improvement in general condition immediately. 6.4.40: Became severely pyrexial and M & B 693 (aqueous) given intramuscularly. Temperature normal by 10.4.40. Stools normal, no vomiting. Rapid gain in weight since.

Acute Toxic Polyneuritis.—J. B. ATKINS, B.M. (by permission of Dr. DONALD PATERSON).

Michael J., aged 8½ years.

4.4.40: Admitted to hospital with one month's history of paræsthesia in fingers and toes, and two weeks' weakness of hands and feet, with pain in calves. No antecedent illness.

On examination.—Central nervous system: Cranial nerves normal. Marked wasting and loss of power in small muscles of hands and feet. Foot-drop. Reflexes: B.J.+, +; T.J. diminished; S.J. diminished; K.J.+, +; A.J.−, −.

Muscle tenderness in calves. Hyperæsthetic bands to all forms of sensation at knee and ankle, diminished sensation below. No posterior column loss. All other systems normal. Reaction of degeneration in maximally wasted muscles.

Cerebrospinal fluid: Cells 2·5 per c.mm.; protein 30 mgm.%. Sedimentation rate: 15 mm. in one hour. Schick test negative. Patient showed steady improvement with physiotherapy.

Bilateral Artificial Pneumothorax for Pulmonary Tuberculosis Two Years after Treatment was commenced.—BERYL D. CORNER, M.D.

E. B., aged 11 years, female.

Past history.—Healthy.

Family history.—Only child. Mother died of pulmonary tuberculosis in 1936.

History.—July, 1937, brought to out-patient department of Bristol Children's Hospital for enuresis of two years' duration. Urine and intravenous pyelograms normal; skiagram of chest showed slight mottling in right mid-zone. Admission advised but patient was

lost sight of. January 1938 : Admitted as emergency to surgical ward with acute vulval abscess. Pyrexia failed to subside after adequate drainage, and signs of consolidation were then detected in the right upper lobe. Tubercle bacilli were found in the deposit from stomach washings.

Patient was kept under observation and on absolute rest for two months. X-rays then showed evidence of cavitation in the right lung and temperature failed to settle. Artificial pneumothorax was induced in May 1938. Mottling became more definite in the left mid-zone and temperature did not settle, so that left artificial pneumothorax was induced in September 1938. Good collapse was maintained until September 1939, when bilateral fluid developed, and the left upper lobe subsequently became adherent.

Adhesions have always been present on the right, but there has been a considerable amount of calcification in the collapsed area.

Patient has been afebrile for three months, has been getting up four hours daily, and has gained 1 st. 3½ lb. in weight during last six months.

POSTSCRIPT (May 1940) Gastric lavage : No tubercle bacilli, and guinea-pig inoculation negative. Sedimentation rate, 10 mm. in 1 hour (Westergren).

[*May* 24, 1940]

***Staphylococcus aureus* Septicæmia with Recovery, treated with M & B 693.**—BERYL D. CORNER, M.D.

R. C., female, aged 10 years.

Past history.—Attacks of cyclical vomiting

History.—9.1.40 : Sudden onset of headache, vomiting, and pyrexia. Temperature 101° F. 11.1.40 : Complained of inability to hold a tumbler in her right hand. Temperature 102° F., slight diarrhœa, delirious at night. 13.1.40 : Increased pyrexia to 103° F., continual delirium, occasional vomiting. 14.1.40 : Admitted to hospital. Toxic appearance, cheeks flushed, temperature 102·4° F. Pulse 130. Respiration 28. Petechial rash present all over trunk. Tongue furred and dry, throat not obviously infected. Only complaint was weakness of the right hand. Slight tenderness was detected over the upper end of the right humerus, and there was limitation of all movements at the shoulder-joint.

Course.—Within twelve hours of admission, red tender swellings appeared on the dorsum of the right foot, and along the radial border of the left forearm. Two days later a similar swelling appeared on the left wrist, which subsided in forty-eight hours. The other two swellings increased in size and became tense and fluctuating. Slight swelling of right upper arm, but very little tenderness.

25.1.40 : Abscess on right foot incised. Large quantity of pus evacuated, first metatarsal felt to be roughened, gauze pack inserted into wound.

30.1.40 : Developed sallow appearance, with slight cyanosis. Pericardial rub detected but no obvious cardiac dilatation. Pain on pressure over 2nd and 3rd right intercostal spaces at sternal border. There was definite deterioration in general condition with anorexia. Swelling on left forearm completely subsided.

Pericardial rub became very loud all over præcordium and persisted till 8.2.40, apex beat moved out to beyond left nipple line. During this week temperature rose to 105° F. and pulse to 160. There was great increase in swelling and tenderness over right humerus. Mr. Eyre-Brook incised this swelling under gas and oxygen anæsthesia on 6.2.40. Necrotic tissue leading down to bone was found and curetted, but very little pus.

10.2.40 : Pain and swelling of right elbow, which subsided after forty-eight hours but recurred again on several occasions during the next four weeks.

13.2.40 : Temperature 99° F. Pulse 96. Great improvement in general condition ; temperature and pulse remained normal.

Patient has been up and walking about for a month. Wounds are healed and there are no abnormal physical signs in the heart. Almost full range of shoulder movements.

Investigations

Blood cultures.—16.1.40: Profuse growth of *Staphylococcus aureus.* 30.1.40: Few contaminants only. 7.2.40: Sterile.

Throat swab.—16.1.40: Vigorous growth of *Staphylococcus aureus.*

Pus from abscess.—25.1.40: Pure growth of *Staphylococcus aureus.*

Blood-counts.—16.1.40: W.B.C. 33,000 per c.mm.; polymorphs. 79%. 11.2.40: Hb. 50%; W.B.C. 5,400 per c.mm.; polymorphs. 68%. 26.3.40: Hb. 113%; W.B.C. 6,000 per c.mm.; polymorphs. 38%.

Catheter urine.—23.1.40: Occasional pus cells; few colonies of *Staphylococcus aureus.* 5.3.40: Sterile.

X-rays.—16.1.40: No abnormality seen in humerus, radius, or metatarsals. 20.3.40: Chest and heart normal. Osteomyelitis upper end of humerus. Suspicious rarefaction upper end of shaft of right radius. Osteomyelitis of first metatarsal.

Electrocardiogram.—7.5.40: Normal.

Treatment.—M & B 693 grm. ½ four-hourly was started immediately on admission and continued for seven days; after an interval of thirty-six hours it was continued in the same dosage for eight days. As the patient seemed to be deteriorating, it was decided to try uleron, but this was badly tolerated, so that M & B 693 was started again and continued until 19.2.40. A total dose of 74¾ grm. was given, and 24 grm. of uleron. Blood transfusions, 200 c.c., were given on 19.1.40 and 8.2.40. Ferri et ammon. cit. gr. xv t.d.s. has been given since 30.1.40.

Cerebral Abscess due to Pfeiffer's Bacillus—Six Years after Pfeiffer's Bacillus Meningitis.—T. G. I. JAMES, F.R.C.S.

L. P., aged 9 years.

Past history.—Meningitis at age of 2 years. Treated at Westminster Hospital by frequent lumbar punctures. Pfeiffer's bacillus isolated from cerebrospinal fluid. Eventual recovery, but with right hemiplegia.

Well until 21.9.39, then became lethargic and irritable, the latter symptom increasingly severe with headache and occasional vomiting. Two months later admitted to Staines Hospital: Lethargic with neck rigidity, and positive Kernig's sign; right hemiplegia; early papillœdema. Temperature 99·6° F. Pulse-rate 120.

Lumbar puncture.—Pressure greatly increased; fluid clear. Protein 100 mgm.%, chlorides 730 mgm.%, cells 26 per c.mm.

Skiagram of skull.—Calcified lesion in left frontoparietal area.

Steady deterioration with increasing lethargy.

1.12.39: Admitted to Central Middlesex County Hospital. Unconscious. Left pupil dilated and fixed, right pupil smaller with sluggish reaction to light. Papillœdema 2 dioptres. Right hemiplegia.

Exploration of left frontoparietal region by burr-hole. Calcified area found under dura mater. Large abscess at depth of 3 cm. from dura, 3 oz. of pus obtained. Consciousness regained. Pfeiffer's bacillus cultured from the pus.

Further treatment.—Repeated aspirations, with attempt at removal of capsule on 14.3.40, after raising osteoplastic flap. Calcified area over cortex removed and found to contain small purulent foci (old subarachnoid circumscribed abscess). Capsule of subcortical abscess too thin for removal. Drainage of abscess cavity by gutta-percha.

Wound now healed: Symptom-free apart from right hemiplegia, which remains unchanged.

Dr. COURT said that first of all in view of the present claims of chemotherapy it must be noted that at the age of 2 this child had survived both a meningitis, due to Pfeiffer's bacillus, and some ninety lumbar punctures involved in the treatment.

The second issue concerned the lesion present during the interval. Apart from two isolated fits the child had remained well for six years. It was unlikely that the extensive cerebral abscess found at operation had been present all the time.

It seemed reasonable to suppose that a small encysted area or areas of suppuration had remained in the subarachnoid space or superficial layers of the cortex, and that extension had taken place towards the end of last year, producing the present condition.

The most remarkable fact of all was that the causal organism of the initial disease had remained alive throughout the whole of the latent period and was capable of vigorous growth on several occasions. Though this was known to be a property of certain organisms such as the tubercle bacillus, Dr. Court was not aware that Pfeiffer's bacillus belonged to this group.

Congenital Eventration of the Right Half of the Diaphragm (Specimen).—J. SAKULA, M.D.

Peter E., the first child of unrelated parents.

History:—Normal birth but there was some difficulty in starting respiration. He required oxygen to keep him a good colour. No difficulty in feeding and no cough or dyspnœa after feeding.

28.12.39 : Admitted to Central Middlesex County Hospital. Aged 5 weeks. Condition very cyanosed with respiratory distress. Trachea and heart displaced to the left. Marked dullness over the whole of the right side of the chest.

Progress.—Cyanosis persisted and became worse with increased distress whenever oxygen was stopped. No distress after feeding. Seemed easier when lying on right side or flat. General condition became weaker and after several attacks of extreme distress the child died at the age of 6 weeks.

X-ray examination.—Right side of chest completely opaque. Stomach in normal position, and gas outlined intestine in lower part of right chest above normal level of diaphragm.

Post mortem.—Eventration of the right dome of the diaphragm with the right side of the chest occupied mainly by right lobe of liver.

Osteopetrosis (Albers-Schönberg Disease) in an Infant of Two Years.—REGINALD LIGHTWOOD, M.D., and E. ROHAN WILLIAMS, M.D.

John P., male, 2 years, has shown symptoms of anæmia and weakness from about 3 months old.

Family history.—One older child, healthy. Parents not related. No history of inheritance of condition.

Examination at age of 6 months (October 1938).—Small and backward, weight 10 lb., marked hypotonia and skeletal changes, presumed at the time to be rachitic, namely, enlarged epiphyses, rosary, Harrison's sulcus, enlarged skull with wide fontanelle (? hydrocephalic). Nystagmus present. Wassermann reaction negative. Hæmatopoietic system : colour, pale and greenish ; spleen 1 in. below umbilicus, liver 3 in. below costal margin. No adenopathy, no ascites, no jaundice. Van den Bergh reaction negative ; fragility of erythrocytes very slightly increased. R.B.C. 2,787,500 ; Hb. 58% ; C.I. 1·0 ; anisocytosis, poikilocytosis, polychromasia, 10 nucleated red cells per 100 leucocytes, reticulocytosis 15—20%, mean cell diameter normal. W.B.C. 13,500 ; differential—normal ratio.

Course.—The anæmia has resisted treatment, normoblasts are still seen, and usually there are 2 to 3% of myelocytes. November 1939 : R.B.C. 3,900,000 ; Hb. 60% ; C.I. 0·8 ; W.B.C. 9,800.

Recent clinical examination (May 1940).—A dwarfed, anæmic, and apparently mentally defective infant. Skull enlarged and markedly dolichocephalic, prominent frontal elevations. Bilateral proptosis, left ptosis. Primary optic atrophy. Nystagmus. Liver enlarged, spleen enlarged and hard. Scoliosis.

Radiological report (E. Rohan Williams).—Selected radiographs of the skeleton show a striking generalized change due to osteopetrosis. The appearances are typical in the sense that they show several features to which attention has been drawn in different cases by various authors. Particular attention may be drawn in this case to :—

(*a*) The marked clubbing at the ends of the shafts of the long bones—especially lower femora, upper tibiæ and lower radii (Plate I, figs. 1 and 2).

(*b*) The vertical fissuring in the metaphyseal zones described by Brailsford (fig. 2).

(*c*) The sclerosis at the base of the skull, together with marked thickening of the frontal bone, moderate hydrocephalic disproportion of the skull to the face, and dolichocephalic shape of the head ; also clubbing of the posterior clinoid process (Plate II, fig. 3).

(*d*) The dense sclerosis in the ribs and vertebral bodies (Plate II, fig. 4).

The most interesting feature of clinical significance is the degree of "petrosis" in the medullary cavity of the long bones : this is well seen in the femoral shafts and the appearance strongly suggests that the abnormal bone has been laid down apart from any cortical growth. The degree of osteopetrosis is most unusual for the age of the patient and one would anticipate a rapid and severe anæmia.

The sister of the patient was radiographed (knee-joints and femora) and no abnormal changes were seen.

Comment.—Osteopetrosis is a congenital condition in which symptoms are not always present in early life, but when they do appear, they tend to progress. The anæmia is due to sclerosis within the medullary cavity of the bones, and there follows a compensatory over-activity of residual marrow and extramedullary hæmatopoiesis. Signs of such changes are well seen in this patient who shows reticulocytosis, normoblasts in the blood, enlargement of liver and spleen. Further, osteosclerotic changes at the base of the skull produce cranial nerve paralyses, and optic atrophy is especially common.

The ætiology of osteopetrosis awaits elucidation. The bone changes indicate a disturbance of calcium metabolism, and this is supported by the finding in certain cases of metastatic calcification in vessels, tendons, skin, and myocardium (Schulze, Alexander). Dupont (1930) suggests that it is a manifestation of hyperparathyroidism, and Ellis (1934) says that the balance of evidence favours a parathyroid origin.

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DUPONT, J. " L'Ostéopétrose " (Thèse), Lyon, 1930.
ELLIS, R. W. B. (1934), *Proc. Roy. Soc. Med.*, **27**, 1563 (Dis. in Child., 67).

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PLATE I.

FIG. 1.

FIG. 2.

REGINALD LIGHTWOOD and E. ROHAN WILLIAMS: Osteopetrosis (Albers-Schönberg Disease) in an Infant of Two Years.

PLATE II.

FIG. 3.

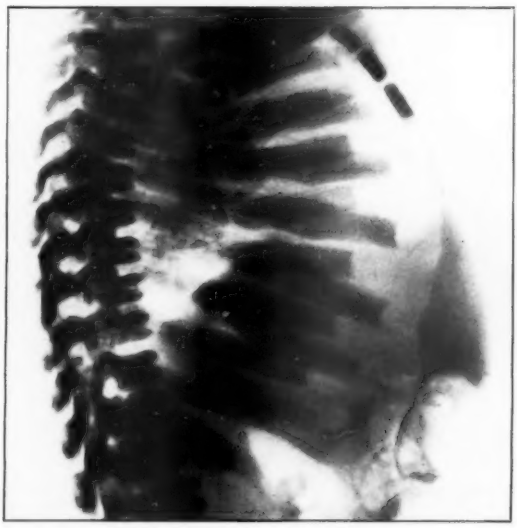


FIG. 4.

REGINALD LIGHTWOOD and E. ROHAN WILLIAMS: Osteopetrosis (Albers-Schönberg Disease) in an Infant of Two Years.

Section of Anæsthetics

President—HAROLD SINGTON, M.D.

[*May* 3, 1940]

A Method of Administering Continuous Intravenous Anæsthesia for Abdominal Surgery

By L. CARNAC RIVETT, M.Ch., and GEORGE QUAYLE, M.R.C.S., L.R.C.P.

Assembling of apparatus.—The apparatus, having been sterilized in a drum, is fitted up on to a stand which is clamped on to the leg of a trolley. The ordinary 5% pentothal is diluted down to a 2% solution with sterile water, and placed in the graduated pentothal container. The rubber tubing and "Y"-piece glass connexion are then filled with the solutions, precautions being taken to eliminate all air bubbles. When connecting the Hamilton-Bailey needle to the two-way adaptor, it is wise to fix them together by means of a sterilized elastic band to prevent any risk of their slipping apart with slight movements of the arm or rubber tubing.

Induction.—Venous puncture is performed with a Hamilton-Bailey needle, connected by means of a two-way adaptor to a 10 c.c. syringe and the drip apparatus. 10 c.c. of 1 : 20 pentothal solution (0·5 grm.) is then injected slowly over a period of two or three minutes. The tap of the two-way adaptor is switched over to the drip apparatus and dextrose and saline mixture is allowed to run into the vein at the rate of 40—50 drops per minute. This prevents blood clotting in the needle. After removal of the syringe, the needle and "Y"-piece connexion are kept in position by means of adhesive strapping. An airway is inserted and respirations are made more obvious by means of a piece of cellophane paper, 3 in. square, strapped on to the nose and chin. The movements of this paper and its change from clear to dim can be easily observed from a distance. The patient is now wheeled into the theatre and transferred to the operating table. The arm is abducted to a right-angle and fixed in this position by means of a special arm-rest, which does not interfere with the surgeon's movements, and which enables the patient to be moved, without further adjustments, into the Trendelenburg or other positions. Before the initial incision is made, the depth of anæsthesia can be verified by pricking the skin with a sharp needle. The time occupied in the performance of this whole procedure usually takes between five to ten minutes.

Maintenance.—Throughout the course of the operation, saline and dextrose are kept dripping to ensure that the needle is always patent. If, at any stage of the operation, the patient shows signs of shock, the rate of flow can be increased, and if considered necessary, the apparatus can remain attached to the arm during the patient's return to the ward. In the event of any severe hæmorrhage, blood could be substituted for the saline.

Owing to the dilution of the pentothal down to a 2% solution, the amount given can be delicately controlled. 2—10 c.c. of this solution are usually required every two to ten minutes. The indications of light anæsthesia are usually well marked.

When these indications are observed, 5 c.c of 2% pentothal solution may be safely given, and within 30 seconds the facial grimaces will have disappeared and the groaning subsided to a quiet and even respiratory movement. No further pentothal solution is now given until the signs of light anæsthesia reappear which takes between two to ten minutes. Even when these signs again become evident, there is no

alteration in the relaxation of the abdominal muscles or any increase in the respiratory excursion of the bowels. This moment can thus be waited for without fear of any hindrance to the surgeon, and with the knowledge that the patient can be pushed, safely and quickly, back to the stage of deep anæsthesia. Although it is impossible to estimate the amount of pentothal necessary to cause signs of serious respiratory distress, there is a wide margin of safety between the stage of adequate anæsthesia and that of overdosage. Coramine, carbon dioxide and oxygen are always kept at hand. In an emergency, 5 c.c. of coramine should be injected into the rubber tubing near the vein.

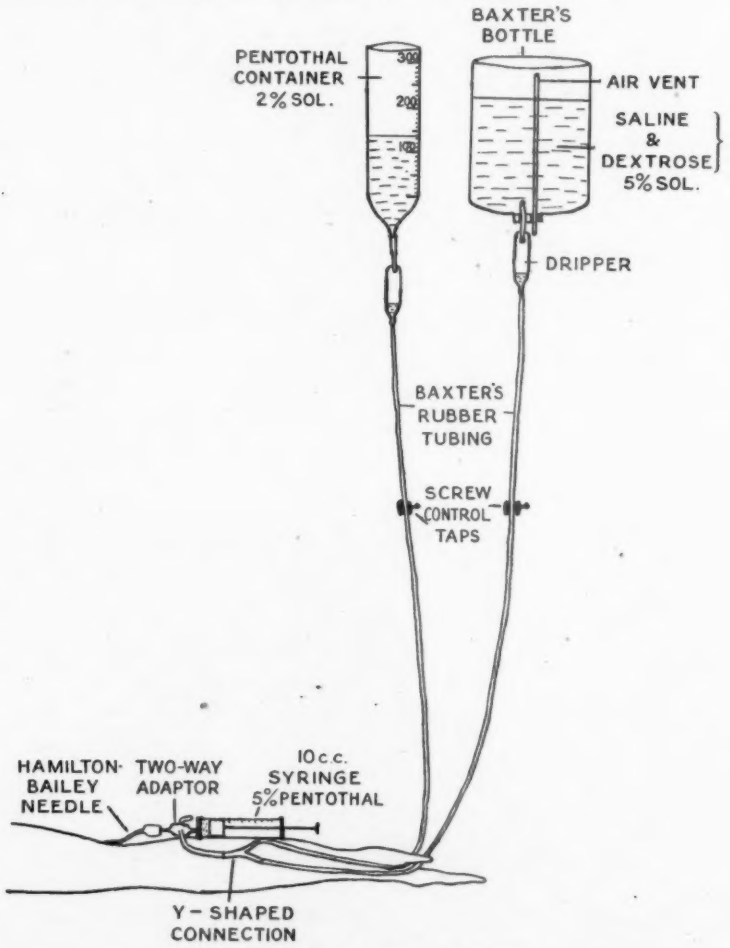


Diagram of Double Drip Apparatus.

It is only necessary between cases to detach and sterilize that portion below the "Y"-shaped glass connexion and refit another, thus reducing the interval between cases to a minimum. Further, should the patient be lightly under at first or become so during the operation, deep anæsthesia can always be produced in 30 seconds.

A SUMMARY OF FIFTY ABDOMINAL OPERATIONS PERFORMED UNDER CONTINUOUS INTRAVENOUS ANÆSTHESIA [1]

No. and Age	Operation	Duration of anæsthesia	Total evipan used	Post-operative remarks: Nausea	Vomiting	Restlessness	Recovery of consciousness	Amnesia	Cough	Headache	Difficult and unsuccessful cases: Difficulty encountered	Reason	How overcome
1 35 yrs.	Cæsarean section	15 min.	1·6 grm.	—	—	—	1½ hrs.	3½ hrs.	—	—	—	—	—
2 49 yrs.	Total hysterectomy	35 min.	4 grm.	+	+	—	3½ hrs.	12 hrs.	—	—	—	—	—
3 43 yrs.	Total hysterectomy	30 min.	2·9 grm.	+	—	—	1 hr.	7 hrs.	—	—	—	—	—
4 43 yrs.	Ovarian cyst (v. big)	20 min.	1·4 grm.	—	—	—	2 hrs.	10 hrs.	—	—	—	—	—
5 49 yrs.	Pan-hysterectomy	30 min.	1·6 grm.	+	—	—	2 hrs.	6 hrs.	—	—	—	—	—
6 50 yrs.	Total hysterectomy	25 min.	2·2 grm.	++	++	+	?	?	—	+	Evipan container fell and broke	Carelessness	Container cut away. Continued with syringe into cut end of tubing
7 40 yrs.	Ovarian cyst (v. big)	25 min.	2·74 grm.	+	—	+	?	?	—	—	Cyanosis. Shallow respirations	Overdosage	—
8 31 yrs.	Shortening round ligaments L. oophorectomy, appendicectomy	35 min.	4·6 grm.	+	—	—	?	?	—	—	Light at first	—	—
			Total pentothal used										
9 40 yrs.	Total hysterectomy	35 min.	1·06 grm.	+	+	—	1½ hrs.	6 hrs.	—	—	—	—	—
10 48 yrs.	Inoperable ovarian tumour	35 min.	0·94 grm.	—	—	—	1 hr.	4½ hrs.	—	—	—	—	—
11 43 yrs.	Sub-total hysterectomy	30 min.	1·1 grm.	+	+	—	?	?	—	—	—	—	—
12 37 yrs.	Total hysterectomy	45 min.	1·1 grm.	—	—	—	?	?	—	—	—	—	—
13 38 yrs.	Laparotomy	25 min.	0·675 grm.	+	—	—	?	?	—	—	—	—	—
14 36 yrs.	Myomectomy	40 min.	1·4 grm.	—	—	—	?	?	—	—	—	—	—
15 34 yrs.	Ovarian cyst (v. big)	50 min.	1·05 grm.	+	+	—	1 hr.	2 hrs.	Increased	—	Laryngospasm Cyanosis. Shallow res. Feeble pulse Poor relaxation	Airway under 7 c.c. Unilateral A.P. Ovarian cyst	Removed airway Artificial Res. CO_2 and O_2 Coramine 2 c.c
16 20 yrs.	Appendicectomy	23 mins.	0·8 grm.	—	—	—	?	?	—	—	Missed vein twice	—	—
17 49 yrs.	Sub-total hysterectomy	48 min.	1·32 grm.	—	—	—	?	?	—	—	—	—	—
18 48 yrs.	Sub-total hysterectomy and ovariotomy	45 min.	1·2 grm.	—	—	—	?	?	—	—	—	—	—
19 45 yrs.	Sub-total hysterectomy	?	?	+	+	—	?	?	—	—	Rigid and light. Not dripping properly	Needle not properly in vein	Abandoned drip. Continued with G.O. and E.
20 50 yrs.	Sub-total hysterectomy	45 min.	1·3 grm.	+	—	—	2 hrs.	4 hrs.	—	—	—	—	—
21 46 yrs.	Laparotomy, omental tumour	65 min.	1·41 grm.	+	—	—	3 hrs.	6 hrs.	—	—	—	—	—
22 38 yrs.	Shortening round ligaments, endometriosis	45 min.	1·71 grm.	—	—	—	1½ hrs.	4 hrs.	—	—	—	—	—
23 41 yrs.	Myomectomy	30 min.	1·2 grm.	+	—	—	2 hrs.	5 hrs.	—	—	—	—	—
24 40 yrs.	Ventral suspension	40 min.	1·35 grm.	—	—	—	1½ hrs.	7½ hrs.	—	—	—	—	—

[1] Evipan used in Cases 1-8 ; pentothal used in Cases 9-50.

No. and Age	Operation	Duration of anæsthesia	Total pentothal used	Post-operative remarks: Nausea	Vomiting	Restlessness	Recovery of consciousness	Amnesia	Cough	Headache	Difficult and unsuccessful cases: Difficulty encountered	Reason	How overcome
25 30 yrs.	Shortening round ligaments	40 min.	1·05 grm.	—	—	—	1½ hrs.	2½ hrs.	—	—	—	—	—
26 46 yrs.	Total hysterectomy B.P. 220/140	73 min.	1·51 grm.	+	+	—	1 hr.	3 hrs.	—	—	Missed vein in left arm	—	Used rt. arm
27 39 yrs.	Total hysterectomy	31 min.	1·0 grm.	+	—	—	2½ hrs.	7 hrs.	—	+	Film taken	—	—
28 49 yrs.	Bilateral salpingo-oophorectomy, appendicectomy	34 min.	1·29 grm.	—	—	—	1 hr.	3½ hrs.	—	—	—	—	—
29 51 yrs.	Examination under anæsthesia. Total hysterectomy	47 min.	0·96 grm.	+	—	—	1 hr.	7 hrs.	—	—	—	—	—
30 45 yrs.	Examination under anæsthesia. Total hysterectomy	98 min.	2·68 grm.	+	—	—	2 hrs.	8 hrs.	—	—	—	—	—
31 36 yrs.	Myomectomy	45 min.	1·35 grm.	+	++	+	1 hr.	?	—	—	Hysterical before and after operation		
32 52 yrs.	Sub-total hysterectomy	28 min.	0·86 grm.	+	+	—	½ hr.	1 hr.	—	—	Vomited during operation	—	—
33 27 yrs.	Appendicectomy	35 min.	1·16 grm.	—	—	—	½ hr.	1½ hrs.	—	—	—	—	—
34 55 yrs.	Total hysterectomy	55 min.	1·14 grm.	+	++	—	1½ hrs.	4 hrs.	—	—	Cyanosis of face	Dilated facial capillaries	—
35 44 yrs.	Total hysterectomy	55 min.	1·0 grm.	—	—	—	6 hrs.	12 hrs.	—	—	Hb. 40%	Menorrhagia	Blood substituted for saline. 2 pints given during and after op.
36 36 yrs.	Total hysterectomy	35 min.	1·26 grm.	+	+	—	2 hrs.	6 hrs.	—	—	—	—	—
37 43 yrs.	Total hysterectomy	53 min.	1·33 grm.	+	+	+	3 hrs.	7½ hrs.	—	—	Vomited 3 times during op.	—	—
38 63 yrs.	Total hysterectomy	52 min.	1·0 grm.	+	—	—	7 hrs.	20 hrs.	—	—	Very pale	Shock	700 c.c. saline given during operation
39 35 yrs.	Cæsarean section, fundectomy	20 min.	0·91 grm.	?	?	?	?	?	?	?	—	—	—
40 46 yrs.	Sub-total hysterectomy	32 min.	1·1 grm.	+	++	—	2 hrs.	8 hrs.	—	—	—	—	—
41 50 yrs.	Examination under anæsthesia. Total hysterectomy	50 min.	—	+	+	—	2 hrs.	6 hrs.	—	—	Not dripping properly	Needle slipped out of vein	Abandoned drip. G.O.& E. started after examination under anæsthesia
42 40 yrs.	Total hysterectomy	45 min.	1·36 grm.	+	+	—	1 hr.	5 hrs.	—	—	—	—	—
43 31 yrs.	Ovarian cyst (v. big)	22 min.	0·9 grm.	+	—	—	1 hr.	4½ hrs.	—	—	—	—	—
44 45 yrs.	Total hysterectomy	40 min.	1·5 grm.	+	—	—	1½ hrs.	4 hrs.	—	—	—	—	—
45 40 yrs.	Laparotomy, adhesions	60 min.	1·275 grm.	+	+	+	1 hr.	10 hrs.	—	—	—	—	—
46 29 yrs.	Myomectomy	37 min.	1·54 grm.	+	—	—	½ hr.	2½ hrs.	—	—	Missed vein once	—	—
47 49 yrs.	Total hysterectomy	40 min.	1·25 grm.	+	—	—	1½ hrs.	5 hrs.	—	—	—	—	—
48 41 yrs.	Total hysterectomy	45 min.	1·1 grm.	+	—	—	1 hr.	1½ hrs.	+	—	—	—	—
49 26 yrs.	Ectopic gestation	23 min.	1·3 grm.	—	—	—	2½ hrs.	4 hrs.	—	+	Light at first. Patient moved during incision	—	—
50 39 yrs.	Total hysterectomy	24 min.	1·2 grm.	—	—	+	1 hr.	10 hrs.	—	—	—	—	—
		AVERAGE.											
42 yrs.		38.3 min.	1·22 grm.	63%	37%	8%	1¾ hrs.	5¾ hrs.	6%	4%			

ANALYSIS OF CASES

Hysterectomies	28
Oophorectomies	6
Myomectomies	4
Shortening round ligaments	4
Laparotomies	3
Cæsarean sections	2
Appendicectomies	2
Ectopic gestation	1
	50

SUMMARY OF CASES

The tabulated chart consists of 50 consecutive and not picked cases; the only contra-indication being the absence of a suitable vein. The patients varied greatly in general fitness with ages ranging between 20 and 63 years, and blood-pressure between 110/70 to 220/140 mm. Hg. The operations, including 28 hysterectomies, were all of a major character, for which good relaxation was essential. The duration of anæsthesia varied between 15 and 98 minutes (average 38 minutes), and the quantity of pentothal used between 13·5 and 53·6 c.c. (average 24·32 c.c.).

Special note has been made of the difficulties encountered during the administration. No fatalities occurred. In three cases only (Nos. 15, 19 and 41) were any serious difficulties experienced., No. 15 was due to insufficiency of functioning lung tissue, Nos. 19 and 41 due to the needle not being properly retained in the lumen of the vein. The operative risk in patient No. 35 (total hysterectomy with hæmoglobin 40%) was serious. The substitution of blood for saline, thus enabling two pints of blood to be given from the drip apparatus both during and after the operation, was undoubtedly helpful. She made an uninterrupted recovery and was discharged from hospital in seventeen days. Patient No. 26, who had a blood-pressure of 220/140 showed no ill-effects, either during or after the operation. In Cases 1 and 39, of Cæsarean section, it was clearly demonstrated that the passage of pentothal through the placenta to the child is slow. Both children cried immediately upon delivery, which took less than three minutes. The firm and rapid contraction of the uterus under this form of anæsthesia definitely diminishes the amount of bleeding and makes it unnecessary for pituitrin to be given.

The recovery period is more pleasant than with inhalation anæsthesia. All patients who have experienced both, emphatically confirm this statement. Nausea and vomiting are difficult to eliminate, especially in nervous patients and those in whom much handling and exposure of the bowel has taken place; but it can be said that the number of cases of vomiting which does occur is not of the disturbing and sickening nature as that experienced after ether anæsthesia. With the exception of Case 15 (unilateral artificial pneumothorax for pulmonary tuberculosis) whose pulmonary symptoms were slightly increased after the operation, no instance of serious post-operative cough or of chest complications was encountered. Restlessness occurred in 8% and headaches of a mild nature and of short duration in 4%. After return to the ward recovery of consciousness took place in an average of 1¾ hours. This was followed by a period of amnesia lasting for an average of 5¾ hours.

Mr. Carnac Rivett: I have had a very large experience of major pelvic operations under intravenous pentothal, without any inhalation anæsthetic whatsoever, and I can definitely say that there are certain great advantages. Perhaps the first of these is the shallow respiration which accompanies anæsthesia with intravenous barbiturates—a very great advantage in pelvic surgery, as the intestines gravitate into the upper abdomen when the patient is in the Trendelenburg position, giving excellent access to the pelvic organs.

I have found even light anæsthesia gives very good relaxation of the abdominal muscles, and should I demand a little deeper anæsthesia, it is easily and rapidly produced.

It does not appear to be easy for the anæsthetist to know with certainty the depth of anæsthesia, and at one time, as a routine, I tested the patient's insensibility by pricking with a scalpel. I find the more experienced the anæsthetist, the less necessity there is for

this method. It is a minor drawback which is overcome with experience. The second drawback is the occasional difficulty the anæsthetist experiences in finding a vein and in keeping the needle in the vein when found. The only other drawback I have ever seen has been due to some of the solution leaking into the subcutaneous tissues, causing actual ulceration which may take longer to heal than the major operation incision itself.

The anæsthesia does not seem to be as deep as full surgical ether anæsthesia. Therefore, the surgeon must be gentle in all his manipulations. Sudden and violent traction on any organ may produce sufficient stimulus to break through the anæsthesia and cause the patient to move. If anything, this is an advantage, as I am quite convinced that rough handling of the uterus, ovaries or intestines is a very great factor in producing shock. I am convinced that it is the anæsthetic of choice, and that it is the least dangerous of all anæsthetics.

Apparatus for the Administration of Cyclopropane and Oxygen

Dr. A. Canonico demonstrated an apparatus for the administration of cyclopropane and oxygen. This apparatus had been presented to the anæsthetists of Great Britain through the kind offices of Professor Arce, Dean of the Medical Faculty of Buenos Aires and was transmitted through the British Council. The purpose of the gift was to demonstrate the sympathy of the Medical Profession of the Argentine with the Allied Cause.

The Cyclopropane Apparatus Modelo del Instituto de Clinica Quirurgica de Buenos Aires consists of a water depression flowmeter bottle, yoke for cyclopropane cylinder, union for an oxygen cylinder, the latter cylinder forming a support for the apparatus, and a Waters soda lime canister for to and fro breathing, also a simple bubble-through ether bottle.

Fine adjustment valves control the flows of oxygen and cyclopropane, the flowmeters for which are calibrated to 800 and 700 c.c. respectively, and incorporated in the apparatus is an oxygen by-pass, whereby larger flows of oxygen can be administered direct to the mask. The patient's inhalations and expirations can be passed either through the soda lime or direct by means of a valve operating a by-pass in the canister.

A special reducing valve is incorporated in the apparatus so that the pressure of oxygen can be limited to ensure a more steady flow and also to prevent heavy flows being passed through the flowmeter bottle. A safety device, consisting of a blow-off rubber tube connexion, is also incorporated.

Auto-Anæsthetic Apparatus.

Dr. T. B. Jobson demonstrated an auto-anæsthetic apparatus which he had designed and used for many years. Though this apparatus was originally designed for administering anæsthetics for nasal operations, it can be used for any type of operation and can be adapted for intratracheal anæsthesia (*see Brit. M. J.*, 1939 (i), 1110).

Section of Proctology

President—J. P. LOCKHART-MUMMERY, F.R.C.S.

[*May* 8, 1940]

DISCUSSION ON THE SURGICAL TREATMENT OF IDIOPATHIC ULCERATIVE COLITIS AND ITS SEQUELÆ

Mr. Lionel E. C. Norbury : Idiopathic ulcerative colitis, or to be more accurate, ulcerative colo-proctitis, since in the majority of cases the rectum is also involved, is a condition in which examination of the fæces reveals no specific causative factor and the patient's serum fails to agglutinate any of the various strains of *B. dysenteriæ*. There is no doubt that a certain percentage of early cases can be cured or at any rate relieved by medical means alone. In the larger number, however, the disease becomes chronic or progresses with greater or lesser rapidity towards a fatal issue. When one examines the colon of a well-established case it is difficult to imagine how a cure can ever be effected whilst fæces stagnate in the bowel.

The surgical treatment may conveniently be divided into :—

(1) Methods employed primarily for the purpose of colon irrigation, namely appendicostomy and valvular cæcostomy.

(2) Methods directed to exclusion of the colon from the passage of fæces by means of a terminal ileostomy.

(3) Ileostomy followed by colectomy with anastomosis of the ileum to the rectum, or ileostomy followed by excision of the colon and rectum.

My own experience in the surgical treatment of ulcerative colitis has been chiefly confined to appendicostomy. Several of these cases have been virtually cæcostomies since it was found impossible to utilize more than the stump of the appendix.

Analysis of cases.—During the past ten years, I have performed appendicostomy on 20 cases at St. Mark's Hospital and on 7 cases at the Royal Free Hospital. Of these 4 died—26 days, 1 month, 7 weeks and 6 months respectively after operation.

The general health of the remainder has gradually and steadily improved as also have the sigmoidoscopic appearances, which show a return to normal in a considerable proportion and a marked improvement in most of the rest. The patients have put on weight. I have had the opportunity of following the cases up and examining them with the sigmoidoscope periodically.

Five of these patients reported at hospital within the last few days, and also a patient not included in the series upon whom I operated thirteen years ago.

(1) Mr. B., aged 54. Severe granular colo-proctitis; marked intestinal colic; extreme wasting. Considered a poor operative risk.

November 1, 1938: Appendicostomy. Irrigation for nine months. No irrigation since August 1939. Now has no symptoms. Has put on 3 st. in weight. Normal sigmoidoscopy. He is still keeping the appendicostomy open.

(2) Mr. C., aged 44. Granular colo-proctitis with ulcers. Appendicostomy five and a half years ago. Irrigation for eighteen months. Appendicostomy allowed to close four years ago. No symptoms since. Normal sigmoidoscopy at present time.

(3) Mr. W., aged 47. Marked ulcerative colo-proctitis. Appendicostomy over seven years ago. Irrigation for twenty months. Appendicostomy allowed to close after this period. Symptom-free at present time.

(4) Mrs. R., aged 31. Granular colo-proctitis. Appendicostomy four years ago. Still irrigation once daily. No bleeding but some mucous discharge. Sigmoidoscopy shows marked improvement but still some loss of epithelium in patches.

(5) Mr. C., aged 26. Marked case of ulcerative colo-proctitis. Condition poor. Appendicostomy five years ago. Still irrigation once daily. Sigmoidoscopy; almost normal mucous membrane; a few patches with loss of epithelium.

(6) Mrs. B. Appendicostomy thirteen years ago for severe ulcerative colo-proctitis. Marked improvement for three years and then recrudescence of symptoms suggesting a perforation. Extremely ill with acute abdominal symptoms. Appendicostomy irrigations recommenced with slow but steady recovery. No irrigation for past six years. At present time health excellent and normal sigmoidoscopic appearances. Appendicostomy kept.

It is interesting to note that after appendicostomy the sigmoidoscopic appearances tend to remain *in statu quo* for some considerable period although the general condition is markedly improved.

Appendicostomy should be more extensively used for irrigation purposes not only in late cases of ulcerative colitis but in those of moderate severity which have resisted a short course of purely medical treatment. There should be closer co-operation between physician, pathologist and surgeon in dealing with such cases. Appendicostomy is of little use when the patient is moribund.

Irrigation of the colon and rectum from the upper end by means of an appendicostomy is obviously better than irrigation *per rectum* against the stream.

Satisfactory colonic lavage from the rectal approach requires the services of an expert and is difficult at the best of times but may be positively dangerous in cases of ulcerative colo-proctitis. The so-called "high colonic lavage," in which a long tube is passed into the rectum with the idea that it has traversed the colon, is a fallacy. It is almost impossible for such a tube to be passed blindly higher than or even as high as the recto-sigmoidal junction since it curls up in the rectum. This can be proved by X-rays. The presence of such a tube may seriously damage the already diseased bowel wall.

Irrigation of the whole colon can be accomplished through a tube passed for a distance of 3 to 4 in. into the rectum with the patient in different positions to allow gravitation of the fluid to different portions of the large bowel. It is, however, a tedious process and requires expert knowledge and skill.

With an appendicostomy a patient can irrigate the colon himself with great ease.

In the surgical treatment of ulcerative colitis appendicostomy is the method of choice in cases of moderate severity. Experience has taught me certain points in technique :—

(*a*) Local anæsthesia is satisfactory.

(*b*) A small muscle-splitting incision suffices.

(*c*) The blood supply to the proximal portion of the appendix must be carefully preserved. It is often quite unnecessary to divide any portion of the meso-appendix in order to bring the appendix to the surface. Careful division of the fine adhesions or membrane surrounding the meso-appendix will usually allow sufficient mobilization to fashion a satisfactory appendicostomy.

If the appendix is considered suitable, the caput cæci is anchored to the edges of the peritoneal incision.

(*d*) Unless the patency of the appendix is in doubt, it is wise not to open it at the time of operation since there is a tendency for the wound to become infected and slough, and the vitality of the appendix may be endangered.

(*e*) In many cases, even if the appendix appears narrow and its lumen precarious, I have

found that if left unopened for a week the appendix will often become distended in the interim and its lumen much increased.

(*f*) If the distal portion of the appendix is fibrosed, it may still be possible to utilize the proximal end. If the appendico-cæcal valve or valve of Gerlach can be preserved there is much less liability to leakage of fæces than if a valvular cæcostomy is employed.

(*g*) In certain cases, especially in patients with thick abdominal walls, it may be impossible to exteriorize the appendix and produce a satisfactory stoma so that there is a risk of contraction of the channel as it traverses the abdominal wall. The track should be kept open by the regular passage of the catheter morning and evening, even when irrigation has been discontinued.

(*h*) In my opinion it is wise not to close an appendicostomy since experience has shown that cases of ulcerative colitis are liable to relapse. (Cf. case of Mrs. C. Severe ulcerative colitis with well-marked ulcers. Appendicostomy and irrigation for six years. Sigmoidoscopy ; normal mucous membrane. Two months later appendix removed. Relapse within two months.)

In a well-fashioned appendicostomy with a protruding button of mucous membrane, there is no tendency to spontaneous closure, but as already mentioned any cicatricial contraction can be obviated by the regular passage of the catheter.

Solutions employed for irrigation of the colon.—Two pints of normal saline solution morning and evening is usually efficacious. It should be warm and run in slowly to avoid spasm and pain. A solution of pulv. sodium chloride co. is a favourite at St. Mark's Hospital. Hypertonic salt solution is also useful.

One has to be careful not to employ any toxic material which may be absorbed. Even lotio bor. if retained for any length of time in the colon may produce general toxic symptoms. It is the irrigation rather than any particular antiseptic that is of importance.

Four ounces of warm olive oil instilled into the colon via the appendicostomy overnight, followed by a wash-out with normal saline in the morning, is to be recommended. Crude cod-liver oil or a 5% solution of bismuth sub-gallate in cotton-seed oil may be substituted for the olive oil. (Bismuth sub-gall. gr. xxii ; cotton-seed oil, ad ʒj.)

After a few weeks' treatment the patient usually feels and looks better and the temperature gradually subsides. The discharge of blood, mucus and pus rapidly diminishes in quantity.

Irrigation may have to be employed for several months or even years in severe cases. Sigmoidoscopy must be employed from time to time in order to gauge progress.

Blood transfusion either before or after appendicostomy is of great value in cases with profound anæmia.

Valvular cæcostomy.—In cases where the appendix has been previously removed or the appendix is fibrotic and unsuitable for irrigation purposes, a cæcostomy may be performed. This may be of the Senn type as devised for gastrostomy, or after the method of Witzel. In either case leakage of fæcal matter is likely and a solid plug or obturator should be worn. This also keeps the cæcostomy from closing, which it is liable to do since the track is not lined by mucous membrane. An intelligent patient can satisfactorily irrigate the bowel by this means.

Terminal ileostomy.—My personal experience of this treatment is limited to two cases:—

(1) Girl, aged 23, in an almost moribund state with probable peritonitis. Blood transfusion and terminal ileostomy. Died two days later. Post-mortem : Peritonitis. Acute ulcerative colitis. Liver large and fatty.

(2) Female, aged about 56. Marked symptoms with profuse discharge of pus *per rectum* suggesting a pericolic abscess which was discharging into the colon. Swinging temperature, terminal ileostomy followed by blood transfusion. This patient was operated upon recently but is making good progress with fall of temperature and marked amelioration of symptoms.

Ileostomy would appear to be indicated in severe cases with marked general symptoms of toxæmia, abdominal tenderness and distension, profuse discharge of pus *per rectum* and extensive ulceration shown by sigmoidoscopy; also where appendicostomy treatment has been tried and failed.

Physiologists tell us that the lowest portion of the ileum is concerned in absorption of

fluids. It is important, therefore, to fashion the ileostomy as low down as possible in order to preserve this function. Thus a semi-solid action of the bowel is obtained and not a continuous watery discharge.

In my two cases the ileostomy was fashioned on the lines of the Paul-Mikulicz operation with a double-barrel stoma and with the afferent and efferent coils sutured together with a view to subsequent closure by means of an enterotome. It is probable that this is too optimistic a view to take since "Once an ileostomy always an ileostomy" is a more apt dictum.

Colectomy.—I have no experience of this method of treatment for ulcerative colitis. It would appear to be unnecessary in the earlier stages of the disease and dangerous in the later. Also in the majority of cases the rectum is involved and not in a condition suitable for anastomosis with the ileum. Total colectomy including the rectum would seem to be a very hazardous procedure.

Surgical treatment of ulcerative colitis should also include attention to infective foci in the body.

Sequelæ.—(*a*) Perforation with general peritonitis (in my series 1 case); (*b*) Peri-colic abscess sometimes discharging into the bowel (2 cases) ; (*c*) Ischiorectal abscess and fistula (1 case) ; (*d*) Fistula-in-ano (1 case) ; (*e*) Fissure (2 cases) ; (*f*) Colitis polyposa (1 case) ; (*g*) Stricture of colon (1 case) ; (*h*) Fistulous communications with adjacent coils of intestine or with the bladder ; (*i*) Complications the result of toxic absorption, e.g. rheumatism, synovitis, arthritis must also be mentioned.

A Bartholin's abscess was present in one of my cases.

When symptoms suggest a perforation into the general peritoneal cavity, I believe it is wise to give morphia and hope that localization will occur. An abdominal exploration in such circumstances would be highly dangerous owing to the friable state of the bowel.

Ischiorectal abscesses should be dealt with by simple incision, any resulting fistula being treated when the bowel is in a more healthy state.

Strictures are luckily not common after appendicostomy but they do occur. They may be single or multiple and may involve several inches of the bowel.

When multiple, radiography will show the constricted portions with dilatations between giving the appearance of a string of sausages. A short-circuiting operation or colostomy may be necessary for the treatment of such a complication. Colectomy may be deemed advisable.

Conclusion.—It is stated in a well-known American textbook that appendicostomy is of little if any value in the treatment of ulcerative colitis and that as good results may be obtained by colonic lavage *per rectum*, combined of course with medical treatment.

But a follow-up of my own cases has shown most encouraging results, symptoms disappearing with the gradual restoration of the bowel-wall to normal.

If a cure or amelioration of symptoms can be obtained by appendicostomy, the surgeon ought not to condemn the patient to an ileostomy which will probably be permanent, or submit him to the risk of colectomy.

Appendicostomy is a valuable adjunct to medical treatment. Ileostomy should be reserved for advanced disease or for cases where appendicostomy has failed.

Mr. W. H. Ogilvie : The surgery of ulcerative colitis is essentially destructive. It comes in where medicine has failed, and has no place as an adjuvant to medical treatment. Appendicostomy has been warmly supported and there are many series of cases treated by appendicostomy that have done well, but there is no convincing evidence that such cases do any better than with medical treatment alone. Cæcostomy has been advocated to replace appendicostomy, but it is not obviously superior. Neither of these operations rest the colon, nor do they allow it to be washed out in a manner that is convincingly better than washing out from below.

Many cases are arrested by medical treatment. What proportion the successes form to the whole is uncertain, but many patients do return, not to perfect health, but to a state where with reasonable care they can avoid relapses and lead a happy, useful and comparatively active life. To one who is familiar with the anatomy and functions of

the colon this is indeed remarkable. The colon carries out the third stage of digestion; its contents are fluid, solid, or gaseous, and highly bacterial; it contracts only once in a while, but then it does so to some purpose and probably gets up a considerable internal pressure. How a colon which has once been inflamed throughout its coats—and we know that the changes during the active stage of ulcerative colitis are most profound—can carry out any of these functions with fibrous walls and a lining consisting in many places of a single layer of unspecialized cells, is almost beyond comprehension. But there is no doubt that sooner or later, and in most cases sooner, the colon reaches a state from which it cannot recover, even though the infective agent be overcome. Surgery should be invoked before that stage is reached, and not after the patient has become toxic and exsanguinated.

The following are indications and contra-indications to operation :—

Absolute indications.—Stricture of the colon. Polyposis. Fistulæ, particularly in the ischiorectal fossæ.

Presumptive indications.—Repeated severe hæmorrhage. Constant blood loss of lesser degree, needing occasional transfusion to maintain the hæmoglobin level. Continuous bed for a year. A fourth relapse in spite of intervals of reasonable health. A segmental distribution, particularly if it involves the proximal colon only.

In contrast to other presumptive indications which are based on an assumption that the colon is destroyed beyond recovery, this group demands operation while the chance of a functionally successful resection remains.

Contra-indications.—The most important is the fulminating type of case. In these a powerful plea is often put forward for operation, on the view that if the colon is rested in the early stages of an infection, it can recover without gross damage, and can later be allowed to function again. In these, however, the colon infection seems the outcome of a lost resistance, and though ileostomy under local anæsthesia is well tolerated, it does not prevent death from toxic absorption.

The surgical treatment of ulcerative colitis as planned, and as carried to completion in a small number of cases, consists of three steps—exclusion, excision, and restoration. Of these the first, total exclusion of the colon by a transverse ileostomy is the important one. When nothing passes into the colon, not only is it mechanically at rest, but the partly digested remains of various foodstuffs which provide pabulum for the resident bacteria no longer reach it. In these circumstances the infection usually subsides, the discharge from the rectum decreases, ceases to be purulent, and soon dwindles to a small daily excretion of mucus. Bleeding stops. The temperature and pulse settle down to normal, appetite returns and the patient regains weight and strength.

The discharge from the ileum is at first continuous and liquid. There is a certain amount of dehydration, and excoriation of the skin presents a problem, but not a difficult one. American writers lay stress on the loss of fluids at this stage, and many series have a surprisingly high mortality following ileostomy. In my small experience I have not been unduly worried by this problem, but have found that the dehydration is made up by an increased fluid intake, and more than compensated by the rapid disappearance of the toxæmia. Within two or three weeks the efflux is less liquid, and within three to six months it becomes semi-solid, and is passed at intervals of three to four hours rather than continuously.

Colectomy can be undertaken as soon as the patient's general condition has recovered sufficiently to warrant the performance of such an operation. It is surprisingly easy, for since the condition is non-malignant, the vessels are tied close to the bowel, and peritonealization is simple; moreover it is an operation that can be done, if necessary in stages, starting at the cæcum, and bringing the proximal end of the remaining distal segment to the surface.

The third stage, implantation of the ileum in the pelvic colon or upper part of the rectum, according to the scope of the previous colectomy, should be undertaken only when the patient is really well, and when the discharge from the ileostomy is sufficiently solid not to be a nuisance in the rectum, and when the rectum has recovered, if not to normal, at any rate to a state when the mucous membrane is healed and the walls soft. In practice the rectum and pelvic colon usually bear the brunt of the disease, and are

often destroyed beyond recovery by the time the patient has been transferred to the surgeon. Implantation of the ileum into a rectum that is still ulcerated, or that is so damaged that it will ulcerate as soon as it is asked to transmit contents, is definitely worse from the patient's point of view than an ileostomy: it is controlled with more difficulty, and is painful in addition.

If restoration of defæcation is going to be impossible, the need for colectomy disappears. The condition of the patient usually improves so much after ileostomy that it cannot be bettered by the removal of a harmless if useless colon. In one of my cases in which the colon was so destroyed that it had been reduced in places to the diameter of a pencil, Dr. Knott cultivated several sections from the removed bowel and found them to be sterile. It appears then that ileostomy is not only the first but the whole treatment of ulcerative colitis, except in those uncommon cases where the rectum is healthy or nearly so.

I have treated only 17 cases of ulcerative colitis radically, excluding cæcostomy and appendicostomy. Of these 17, seven died, and since this mortality accords ill with my advocacy of surgical treatment, I would refer to it briefly. Five died after ileostomy only; three of these were cases of the fulminating type with a few weeks' history, one died of ileus on the fourth day after operation, one survived two and a half months and died with ulceration of the lower ileum. Of the remaining two, one died after colectomy, the other from peritonitis following implantation of the ileum in the rectum. With more sense three out of the seven cases would have been allowed to die naturally, and three more would not have died at all.

The ten living patients are all in satisfactory condition, that is, apyrexial and able to get about. Eight have a permanent ileostomy, and four of the eight have also undergone colectomy. Two have the ileum re-implanted in the pelvic colon.

I would mention a few technical details connected with ileostomy. I first brought both ends to the surface, sometimes apart, sometimes side by side, with the twofold object of being able to wash out through the distal end, and being able to join the two later if the colon recovered. The first is unnecessary, for the colon recovers so rapidly when it is excluded, that washing out is superfluous and tends rather to favour the absorption of toxins: restoration of continuity is a vain hope, for a colon so damaged as to need ileostomy does not recover sufficiently to function again without risk. Further a double-ended ileostomy has two serious drawbacks; it makes subsequent colectomy a good deal more difficult, and it implies division of the ileum an inch or two further from the cæcum than would otherwise be necessary.

This last point raises the question why the ileum is able to undertake the alien function of water absorption to the point of solidification of its contents. Whenever I asked this question in America, I received the answer that it is dependent on the removal of the large intestine, and the opinion is widely held there that water absorption is under some hormonic control, so that until the whole large intestine, including the rectum, has been removed the ileal contents will remain watery. In my small series this has not been true. The patients in whom I have done ileostomy and nothing else, have settled down, after varying periods, to passing semi-solid ileal "stools" with no irritating effect on the skin. The only patient whose discharge remains persistently watery and irritating after two years, is the only one in whom I have removed the whole large intestine down to the anus. This was not for ulcerative colitis, but for polyposis with hæmorrhage, and I had to remove the last two feet of ileum because they were full of polypi. I now believe that watery absorption is in some way governed by the last few inches of the small intestine, and that division of the bowel even 6 in. from the ileocæcal sphincter is less satisfactory in this regard than one close to the cæcum.

I use a very small and low gridiron incision done under local anæsthesia if necessary. The ileum is picked up and the point where Treves' fold leaves it is selected for section. The mesentery is divided for a full 2½ in., to eliminate the drag of peristalsis. The gut is divided between two controlling clamps, the distal end butt-ended with a double pursestring, and dropped back in the abdomen. A rubber tube of half-inch diameter is passed 2 in. into the proximal bowel, and the cut end tied tightly round it. The

incision is then closed round the ileum so that half an inch of bowel projects above the skin : a catgut skin stitch tied round a bit of mesentery will fix it in position. The rubber tube serves two purposes ; first it keeps the incision clean for the first few days, and second it keeps the lumen of the bowel patent in its passage through the abdominal wall, and forestalls the danger of obstruction during repair. Any tendency to prolapse of ileum later, can be stopped by cutting the opening flush and stitching mucous membrane to skin.

Before the efflux becomes solid, the skin tends to get very sore. The best dressing is aluminium paste [1] ; the next best is fullers' earth. Later the discharge is unirritating, and only a colostomy belt is required. A patient with a well-domesticated ileostomy is on the whole better than one with a colostomy, because there are no unheralded explosions and the discharge is not offensive.

Mr. W. B. Gabriel : In ulcerative colitis the disease is presented to us in various stages from a slight granular procto-colitis to a marked procto-colitis with much pus and blood in the lumen of the bowel, and later still the stage of naked-eye ulceration as seen through a proctoscope or sigmoidoscope. The general condition of the patient varies too between that of apparent perfect health, and that of an almost moribund state, with emaciation, profound anæmia and all the signs of a severe toxæmia. The importance of treatment of ulcerative colitis in the earlier stages of the disease should always be stressed.

The researches of Lium [2] on colonic explants in dogs showed that when grafts of the colon were sutured to the abdominal wall with the mucous surfaces exposed, spasm could be induced by mechanical stimulation, by drugs such as prostigmine, or acetylcholine, which stimulate the parasympathetic nervous system and by dysentery toxin ; spasm of the bowel wall resulted in œdema, hæmorrhages and ulceration of the mucosa of the graft. Lium suggests that spasm may be the chief cause of ulcerative colitis, and stressing the importance of a nervous temperament he states that it is common knowledge that nervousness can produce diarrhœa, and this may well develop until the colon is in an almost constant state of spasm.

If Lium's views are correct we now have an added, and weighty reason for advocating the need for early treatment before irretrievable damage has resulted to the colon from prolonged spasm. At this stage medical treatment is of paramount importance, and many cases of generalized procto-colitis have cleared up well with rest in bed in a quiet environment with sedatives such as luminal, a low residue diet to avoid trauma of the mucosa and vitamin therapy (A, B and C).

Surgical treatment is indicated :—

(1) When in spite of rest in bed and careful medical treatment the patient progressively goes downhill, with loss of weight and strength.

(2) When much blood is being persistently lost *per rectum*, and repeated hæmoglobin estimations show that although temporary improvement is given by blood transfusion, it is followed by a fresh fall in a short time.

(3) When signs of toxæmia develop with an evening pyrexia up to 101° or 102°, when a dry tongue and rapid pulse persist in spite of treatment, or develop while the patient is under medical treatment.

(4) Persistently frequent stools, with disturbance day and night and increasing exhaustion.

[1] Powdered aluminium ... ... 1 part by weight
Zinc oxide ... ... 2 parts by weight
Liquid paraffin ... ... 2 parts by volume

(If a few drops of spirit are added to the aluminium powder before adding the liq. paraffin it becomes easier to mix and less evanescent.)

[2] *Arch. Int. Med.*, 1939, **63**, 210.

(5) The fulminating type of case, in which the illness has only lasted a few weeks and has resulted in a grave condition resembling a "typhoid" state.

Appendicostomy is the safest, easiest, least mutilating and the most rational surgical treatment, particularly in young subjects, and should be done before the disease has advanced too far. Appendicostomy allows the instillation of oil (olive oil or cod-liver oil) into the cæcum and entire colon—a treatment which is sound in principle and is closely allied to the recognized use of olive oil orally in ulceration of the stomach and duodenum when spasm and hypermotility are present.

Treatment so far as the appendicostomy is concerned consists in the instillation of 5 oz. of olive oil or cod-liver oil at night, and a washout with one or two pints of normal saline, or pulv. sod. chlor. co.[3] 2 dr. to 1 pint, or 1 : 4,000 mercurochrome, or permanganate each morning. The appendicostomy is merely one item in the course of the medical treatment which must be carefully supervised, particularly as regards a low residue diet of high caloric value, and the administration of vitamins, iron and liquid paraffin. Blood transfusion is of great value and a regular repetition of the red cell count and hæmoglobin estimation give valuable guidance.

Results in 25 cases of appendicostomy done in St. Mark's Hospital and the Royal Northern Hospital during the last ten years

In two cases an appendicostomy failed to be established. One of these was a woman of 32 with a severe ulcerative colitis of seven years' duration : her abdominal wall was stout and the meso-appendix short so that the appendix was only brought to the surface with difficulty : two days later the appendix was black and gangrenous to below the skin level, and an attempt to insert a catheter into the cæcum failed. The wound healed up and the patient gradually improved on medical treatment and was discharged a month after admission. The other case was a man aged 40 with an acute proctocolitis whose appendix, when cut across a week after operation, proved to be fibrosed and had no lumen. He therefore was also treated medically, and two years later was known to be in very fair health, although one recurrence of symptoms had taken place in the meantime.

Five deaths (ages 22, 26, 32, 39, 41) occurred in hospital with the patients unrelieved by appendicostomy. Two of these were very acute, with symptoms of three weeks' and three months' duration respectively, and the others had had ulcerative colitis for one and a half, two and four years respectively.

There were *ten very good results* with apparently perfect healing of the ulceration and restoration of a pale smooth mucosa, with formed stools and no sign of free blood, pus or mucus.

One noteworthy feature was that seven of these were young subjects of 25 years or less, and in no case had symptoms existed for more than two years.

In a separate group I have placed five others who gained much general and local improvement and were discharged from hospital convalescent. Since then the follow-up over a period of up to ten years has shown that occasional relapses have taken place, with recurrence of muco-pus in the rectum. Sometimes the flare-up has followed a holiday away from home, and is due no doubt to the patient's being obliged to eat unaccustomed food. The average age of these patients was 29, i.e. a little older than in the group of 10 very good results in which the average age was 25.

In three cases the patients showed satisfactory immediate improvement, and were discharged from hospital with appendicostomies, but it has not been possible to ascertain the late results.

Conclusion.—In 23 severe cases of ulcerative colitis in which an effective appendicostomy was established there followed 10 very good results, and at least 5 fair results, with a

[3] Pulv. sod. chlor. co. is composed of equal parts of sodium chloride, sodium bicarbonate, and borax.

further 3 cases improved but untraced later. In my view appendicostomy is a valuable method for promoting healing of the ulceration, and can justly be regarded as a life-saving operation.

Of the patients who died, two had acute and three had extremely advanced chronic ulcerative colitis. They died from toxæmia and not, so far as I know, from perforation.

Note.—Since writing this paper, two of the three untraced patients have been followed up after an interval of nine years and six years respectively after appendicostomy. They are in good health and free from symptoms; hence a total of 12 very good results can now be reported for this series.

Sir Arthur Hurst: It is appropriate that a discussion on ulcerative colitis should be held under the chairmanship of Mr. Lockhart-Mummery, as it was at a meeting of the Royal Society of Medicine thirty-one years ago that the clinical study of the disease was inaugurated by his description of the first sigmoidoscopic observations ever made in this condition—a noteworthy contribution to the "pathology of the living".[1]

Mr. Gabriel has referred to Lium's theory that spasm is the main cause of ulcerative colitis. This is quite untenable. Spasm of the colon is a very common and well-recognized clinical condition both alone and associated with excessive secretion of mucus. But though it may be present on and off for many years it is never followed by ulcerative colitis. On the other hand, ulcerative colitis, in common with diverticulitis and cancer, frequently gives rise to spasm.

The following table shows how successful medical treatment is in the large majority of cases if carried out continuously :—

TABLE I.—CASES OF ULCERATIVE COLITIS WHO RECEIVED SOME FORM OF TREATMENT WHILST AT RUTHIN CASTLE (SPRIGGS) OR IN NEW LODGE CLINIC (HURST) FROM 20 TO 1 YEAR PRIOR TO 1937.

	Ruthin Castle	New Lodge Clinic	Total	Percentage
Quite well	34	32	66	77·6
Not well, but improved and "keeping about"	5	4	9	10·6
Ill	1	1	2	2·4
Dead	5	3	8	9·4
Total	45	40	85	100

Before the last war and again in 1920 I had an appendicostomy performed in several of my cases of ulcerative colitis. But I gradually came to the conclusion that the operation was of little or no value. It can be shown by simple radiological experiments that the cæcum can always be reached by running a pint and a half of fluid *per anum* and that the colon, especially when it is abnormally irritable as in ulcerative colitis, is completely evacuated by this means. There is consequently no advantage in injecting the fluid from above. The injection of olive oil has been recommended by Mr. Gabriel on account of its value in duodenal ulcer, but this depends upon its inhibiting effect on the secretion of hydrochloric acid so the analogy fails. A considerable number of the worst cases I have seen, many of which were subsequently cured by prolonged medical treatment, had already had an appendicostomy performed, but the opening had been allowed to close when no improvement had followed. The majority of the cases included in the statistics which have been quoted this evening would have got well just as quickly without operation with the medical treatment which they all received at the same time.

Ileostomy is the operation of choice. Each case must be judged on its merits before deciding whether the opening should be permanent, the divided ileum should be re-joined

[1] *Proceedings*, 1908-9, 2, Sect. Med., 92.

or ileo-sigmoidoscopy or colectomy should be performed.[5] There are three indications for ileostomy: (1) The only hope for the very rare acute fulminating cases with high temperature and passage of large quantities of pus and blood is ileostomy. Courage is required to operate on such a case, but I have seen an amazing improvement follow within twenty-four hours and ultimate complete recovery, the divided ileum being rejoined some weeks later without any recurrence.

(2) When continuous medical treatment under good conditions for about nine months has led to no real improvement.

(3) Very chronic cases which have already developed fibrous strictures or true or pseudo-polyposis by the time they come under observation.

Very few cases have given any trouble after operation; I have rarely seen the severe diarrhœa and dehydration often mentioned as sequels. This is because I always examine the patient after an opaque meal to see whether there is undue hurry through the small intestine. When this occurs the associated enteritis must be controlled before performing ileostomy. Any looseness which develops later can be controlled by diet and codeine. It is most remarkable how comfortable patients are with an ileostomy. They can lead ordinary lives with full activity, and with a well-made apparatus the ileostomy gives no more trouble than a successful colostomy. Two of my patients were girls of about 20, who were able to play tennis, dance and enjoy life for a couple of years before the stoma was closed, and others were professional business men who are quite reconciled to having a permanent ileostomy.

I disagree with Mr. Ogilvie in one matter only; I think both ends of the divided ileostomy should be brought to the surface some distance apart. When no more blood or pus is passed *per anum* the colon is washed out with water from above and the deposit is examined microscopically. When no red corpuscles or pus cells are present and endoscopy shows a healthy mucous membrane (though the lumen of the empty colon is always very contracted) the colitis can be regarded as healed. An X-ray examination of the excluded colon always shows complete absence of haustration, but this would occur if it were completely healthy, as haustration is the manifestation of the activity of the muscularis mucosæ, the function of which is to mix the colonic contents, so none occurs in an empty non-functioning colon. The mucous membrane may be replaced over large areas by a single layer of flattened epithelial cells, the resistance of which must be very much less than that of a normal mucous membrane. Before a second operation is undertaken the bowel is trained for several weeks by injecting some of the fæces discharged from the ileum through the distal ileostomy opening. The fæces are first diluted with water, and gradually made stronger, till finally the whole of the ileal contents are injected undiluted. If there is no untoward reaction it is safe to rejoin the divided ileum. If, however, the disease is of very long standing and strictures or polypi are known to be present an ileo-sigmoidostomy should be performed instead. In either case there is little risk in the actual operation as the bowel is no longer inflamed. After ileo-sigmoidostomy fæces occasionally regurgitate from the anastomosis into the proximal colon, which should be washed out from the distal ileostomy opening once a week, as most of any water injected by rectum goes into the ileum. It is generally unnecessary to excise the excluded part of the colon.

If a year after performing the ileostomy blood and pus are still being excreted *per anum* the colon should be excised down to a point about 9 in. from the anus. It is then generally possible by local treatment from below, including diathermy cautery for polyps and dilatation of strictures with a rubber bag, to restore the remaining colon sufficiently for the ileum to be joined to it after another interval of several months. If, however, this should not occur, the remaining part of the pelvic colon and rectum can be excised.

I regard surgery on the individualized lines I have described as the most important advance in the treatment of ulcerative colitis in the last ten years.

[5] The majority of my cases have been operated upon by Mr. Gaymer Jones of Windsor, and most of the remainder by my surgical colleagues at Guy's Hospital.

The President gave the figures of his own cases, which were as follows :—

	No.	Cured	Relieved	Died
Appendicostomy	44	21	16	7
	4 of the deaths occurred in children under 12 years of age.			
Cæcostomy	4	1	1*	2

* This case still had a cæcostomy ten years later and a stricture in the rectum.

His own view was that appendicostomy played a very useful part in the treatment of ulcerative colitis. It was a far less serious operation than enterostomy, and the opening was readily closed, whereas most surgeons were agreed that once an enterostomy always an enterostomy.

The President also showed five radiograms of severe stricture following ulcerative colitis.

Mr. Rupert Corbett: We have heard of the satisfactory results following appendicostomy—it is possible that some of these cases would have recovered without it. On the other hand about 20% die, and I think that a considerable proportion of these might have survived if a terminal ileostomy had been performed.

The indications for taking such a drastic step as terminal ileostomy are :—

(1) In certain fulminating cases, where the patient is suffering from a severe decline associated with diarrhœa, wasting, high fever, tachycardia and anæmia, and shows no response to medical treatment.

(2) In recurrent cases where there is no response to treatment as on previous occasions (this would include appendicostomy) and the condition of the patient is becoming serious.

An example of this group was seen in our first case, a woman of 22, who had been suffering from the disease for a year and a half. Her condition was very serious at the outset, and required three to four blood transfusions in the first three weeks of her illness. Three months after the onset, an appendicostomy was performed. Shortly afterwards a spontaneous cæcostomy formed, as a result of an abscess forming round the base of the appendix and rupturing through the skin. Medical treatment was continued in hospital, but she finally reached the stage of becoming absolutely bedridden—lying on a rubber bedpan, with an average pulse-rate of 130, and a loss of weight to 4 st.

After terminal ileostomy she made steady improvement. She was up in six weeks (previously fifteen months in bed) and in three months weighed 8 st., and was living a normal life again.

Unfortunately, not all the cases following have done so well.

I have had six cases of terminal ileostomy. Three are alive and well—four, three, and one year respectively, after operation. The remaining three survived the operation and died after varying periods, three and a half weeks, five weeks, and eight months after operation. One of these developed bronchial pneumonia and empyema. Post-mortem revealed that the greater part of the colon had recovered, only one area of ulceration was present in the cæcum. This was three and a half weeks after operation. Another case died five weeks after operation from a severe hæmorrhage from the colon. The third case developed a pelvic abscess, with probable perforation. This occurred in the eighth month after operation.

There are two important points in technique.

(1) A terminal ileostomy is considered better than an ileostomy in continuity, or double-barrelled ileostomy.

(2) The protection of the skin round the fistula. This is a very difficult problem, and very important to the patient as it is so tender. I advise keeping the bowel closed for twenty-four to forty-eight hours if possible, and then insert a Paul's tube, protecting the skin with zinc cream or tulle gras.

The early fitting of an adequate box is a great help, and Donald Rose of George Street makes a variety of models to suit different patients.

Mr. Michael Smyth was interested to hear the President say that in his experience ulcerative colitis was uncommon under the age of 14 years.

While working at an infirmary after the last war, he had met with two cases which had occurred in the same week in the local district—one in a girl of 7 and the other in a girl of 12 years. He was familiar with the President's account of appendicostomy but did not realize at the time that the appendix should be left for some days before opening. In both cases he had opened the appendix at the time of operation, inserted a catheter and washed out the colon, a tube being inserted into the rectum and irrigation continued until the efflux was clear. Irrigations several times daily were continued until both cases were out of danger. Both were almost moribund on admission, but made remarkable recoveries. His experience of appendicostomy was confined to two other cases in adults, who were not so critically ill and both had progressed satisfactorily, but in these cases the appendicostomy had been retained for periodic irrigation.

He was afraid he differed from Sir Arthur Hurst on the question of applying treatment to the colon from the rectum with olive oil or cod-liver oil. In the majority of cases it can be demonstrated by X-ray that the cæcum can be reached with 1 to 1½ pints of barium emulsion, but he had found it difficult to get olive oil or cod-liver oil particularly to flow in, and in order to make any progress it was necessary to make an emulsion. In some cases of cæcostomy he had tried the experiment of instilling cod-liver oil emulsion into the rectum to see if it could be made to traverse the colon and appear at the cæcostomy, but in no case had he been successful. In cases of ulcerative colitis such treatment was better carried out through an appendicostomy or cæcostomy.

Dr. S. W. Patterson quoted the experience of medical and surgical treatment at Ruthin Castle and emphasized the value of continued medical treatment and of continuing diet, douches and general treatment for anæmia after surgical interference In assessing the results of treatment care was needed, since ulcerative colitis was a complaint with remissions and relapses. The indications for operation were (1) treatment of local (ischiorectal) abscess, (2) operations for washing the colon from above, (3) removal of the affected portion of the bowel. Of a series of 48 cases of ulcerative colitis at Ruthin Castle, nine had died. Eight cases had had operations and one of these died.

Ischiorectal abscess	1
Ischiorectal abscess + ascending colostomy	1
Ischiorectal abscess + two-stage colectomy	1
Appendicostomy	1
Cæcostomy	2
Cæcum excised	1
Colectomy	1 (died)

ADDENDUM

A Review of the Late Results of Ulcerative Colitis in Eighty-nine Cases Admitted to the London Hospital

By Dr. J. M. Vaizey, *Medical First Assistant,* and Mr. E. C. B. Butler, *Assistant Surgeon*

There were 89 patients admitted to the London Hospital during the years 1931 to 1937 inclusive in whom the diagnosis of ulcerative colitis was made by sigmoidoscopy or at necropsy.

These figures include some chronic cases whose first admission had been previous to 1931.

In the present series there were 30 males and 59 females. Nine were under 20; 47 between 20 and 40; 27 between 40 and 60; and six over 60. The youngest was 11 and the oldest 70.

Subsequent Course

Fatal cases.—Of the 81 cases which could be traced 29 are known to be dead. Ten died within three months of the onset of symptoms and a further five within one year, i.e. the immediate mortality was 17% of the total. Five more died within three years, two in from three to ten years and four in periods of over ten years from the onset. In three others the duration of the disease was uncertain.

Post-mortem examinations were obtained on 16 cases. The disease affected the entire large intestine in seven, while in nine the cæcum with the more proximal part of the colon had escaped. The small intestine was normal in all except two where the disease had spread to involve the terminal ileum. Peritonitis was the cause of death in five cases, twice from obvious perforation.

Purulent bronchitis was found in five and empyema in one. Severe anæmia was present in three and in two of these this was clearly due to an acute terminal hæmorrhage. One case developed a septicæmia.

Surviving cases.—Fifty-two cases are known to be still alive and of these 29 were re-examined. In this latter group, five described themselves as completely well; eight had remissions when they felt well and relapses which were severe enough to incapacitate them, and eight had chronic diarrhœa. In three defæcation was difficult owing to stricture ; three others were ill, weak and run down without definite colonic symptoms.

Wasting was noted in seven of them and eight were clinically anæmic.

Sigmoidoscopy revealed active ulceration still present in seven, while eight others showed injected mucosa without ulceration. Polypi were seen in four and strictures in the rectum in three. Three refused to be examined and only three showed a normal rectum.

Of the 23 other cases which had been traced by letter, five had remained well, nine had periodic relapses which were not serious and five had relapsed so badly that they required hospital treatment. It is notable that in some cases these relapses occurred after symptomless periods of as long as eight years. Three others suffered from continuous diarrhœa.

These figures are similar to those in the cases examined and indicate clearly how few (10 cases out of 81) really acquire a lasting freedom from symptoms.

The place of surgery in ulcerative colitis is still undecided. In some cases the condition is not recognized and operations are performed for hæmorrhoids or fistulæ which greatly aggravate the condition. We have seen three such examples in this series. The table gives the results of surgical treatment undertaken to cure or relieve ulcerative colitis. The results appear disappointing but only the gravest or most chronic cases were operated on. When scarring has occurred and strictures have formed it is clear that no satisfactory results will be obtained except by surgery.

Kunath (1936) holds that ileostomy with or without subsequent colectomy is usually the most satisfactory method, though it may be badly tolerated and is inevitably unpleasant. Our limited experience would support this view, though when only part of the colon is affected the procedure is not justified.

The immediate mortality has fallen from 50% in the acute stage to about 20%, but there is still a large remote mortality and an even larger chronic morbidity.

Table of Surgical Results.

Cases operated upon, 26.	Recovered, 16.	Died, 10 (38%).
Laparotomy only	Twice, both died	
Appendicostomy performed	16 times	
	2 of these died within a few days	
	2 others had a cæcostomy and then died	
	1 had subsequent ileostomy and colectomy and ultimately well	
	3 have remained open	
	7 have closed but symptoms of colitis have persisted	
	1 has remained apparently free from all symptoms for five years	

Cæcostomy performed	...	4 times 2 subsequent to appendicostomy, both died 1 performed as primary operation, died 1 has remained permanent owing to stricture
Colostomy performed	...	3 times 1 died within a few days 1 died three years later 1 = a permanent transverse colostomy above the affected part. The patient has improved but still has bloodstained discharge *per rectum*
Ileostomy performed	...	Twice Once with colectomy following an unsuccessful appendicostomy, subsequently well (one year follow up) Once for stricture, slight discomfort but well since (five years)

In conclusion we wish to express our thanks to the physicians and surgeons of the hospital who allowed us to investigate their cases and to Professor Turnbull for allowing us access to the post-mortem records.

REFERENCE

KUNATH, C. A. (1936), *Arch. Surg.*, **32**, 302.

Section of Orthopædics

President—T. P. McMURRAY, M.Ch.

[*April* 2, 1940]

DISCUSSION ON FRACTURES AND DISLOCATION OF THE CERVICAL VERTEBRÆ

Mr. W. J. Eastwood: The first reference to fractures of the cervical spine in medical literature is found in the Edwin Smith papyrus published 2500 B.C., the unknown author dealing very briefly with the condition as follows: "One having a crushed vertebra of his neck, he is unconscious of his two arms and two legs and is speechless. An ailment not to be treated." Some centuries later Hippocrates recognized that the fracture could occur and might or might not be complicated by paraplegia, recommending treatment by traction on the head of the recumbent patient. The accepted treatment of his predecessors consisted of tying the patient upside down on to a ladder which was then violently shaken. Paré, with his sound conservatism, followed on the lines laid down by Hippocrates, but even as late as the nineteenth century it was generally agreed that reduction of these fractures was dangerous and useless. Abernethy says: "They are cases so generally fatal that I am convinced an assembly of older surgeons would doubt that there was a possibility of recovery in any case."

In 1814 a modest article on what must have been one of the earliest laminectomies was published by Henry Cline. The paper itself does not read at all epoch-making but it stirred up such a violent controversy between Sir Astley Cooper and Sir Charles Bell that the interest of the profession was aroused. Little more was heard of this method of treatment during the following fifty years, but during this period several papers appeared surveying the end-results and putting forward tentative suggestions as to treatment. Malgaigne in 1855 first published the method of reduction popularized by Walton in his famous paper of 1889. It is a method which has withstood the test of time and is used with very little modification at the present day. The improvement in the results of treatment of dislocations of the cervical spine following this publication was phenomenal; compare Blasius' figures in 1869 of 92·6% fatality in bilateral dislocation with Langworthy's figures in 1930 of 30% mortality for the same injury. The increase in the number of these accidents during the last ten years, because of the increased popularity of motoring and swimming, has resulted in a spate of literature, the majority of the articles coming from the U.S.A., where the injury would appear to be more common. A survey of the literature shows that the common causes are (1) motor car accidents, (2) diving into shallow water, (3) falling downstairs, in this order of frequency; but the more usual industrial accidents rarely cause damage to the cervical spine. Mechanically the skeleton is peculiarly weak in this region, and it is surprising that injury is not more frequent. The articular and interspinous ligaments are of little protective value and the anterior and posterior common ligaments, although admittedly strong, lose much of their strength by the relatively large size of the intervertebral discs. The comparatively poor interlocking of the articular processes is necessary for free mobility, and it is obvious that the stability of the cervical spine depends largely on its musculature.

Clinically the cervical spine can be divided into two distinct areas, the first two vertebræ and the last five. The presence of the odontoid process of the axis and the transverse ligament posterior to it, the horizontal nature of the articular facets, and the fact that 75% of the rotation of the cervical spine takes place at the atlanto-axial joint make the atlas and the axis a specialized section requiring separate consideration.

Atlas and axis.—There are two main types of injury reported or seen in this area. (1) Injuries of the odontoid process and (2) dislocations or subluxations of the atlanto-axial joint. Injuries associated with the odontoid process can be divided into three sections, (*a*) fracture of the odontoid without displacement, (*b*) fracture of the odontoid with displacement of the atlas on the axis, (*c*) displacement forwards of the atlas without fracture of the odontoid.

Fracture of odontoid process without displacement.—This usually occurs at the base of the odontoid where it joins the main body of the axis, but according to Anderson a similar fracture has been found at the tip or in the centre of the process. The two latter types are rare and only of radiological interest, the treatment being symptomatic—rest or light support, such as a paper collar, during the painful stage and graduated use as the discomfort passes away. The fracture at the base of the odontoid, however, is more common and potentially more dangerous. Without displacement it can easily be missed, and instances have been reported of sudden death occurring some time after the accident from sudden displacement forwards of the atlas when the neck was not immobilized. Although these tragedies are extremely rare the possible danger of this complication makes a diagnosis essential. In the absence of displacement, and the more

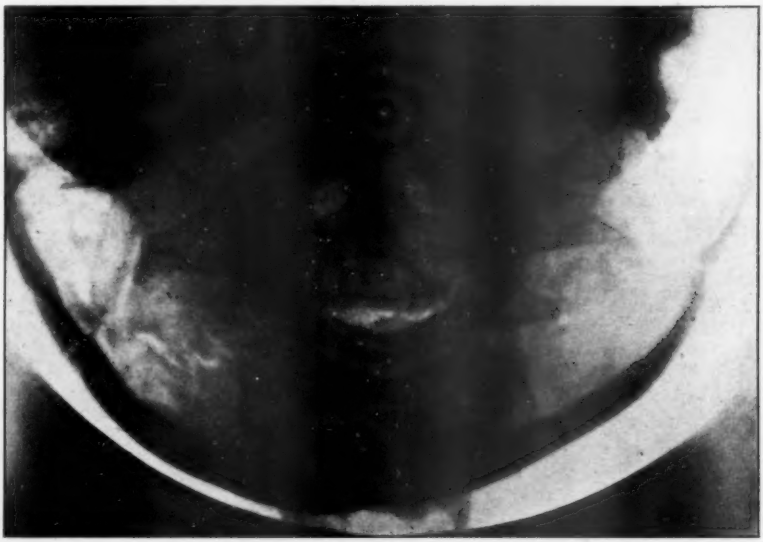


FIG. 1.—Skiagram of an odontoid process taken from above.

than likely vague details of the accident, the clinical picture will be one of limitation of movements, especially of rotation, accompanied by a varying amount of pain. The diagnosis, therefore, rests mainly on the X-ray, and one cannot too strongly emphasize the importance of routine radiography in several planes. A complete radiological investigation of the cervical spine must include an anteroposterior and a lateral view of the whole seven vertebræ, with as much of the first dorsal as possible, and an anteroposterior of the odontoid process. It is usual to take this latter view through the open mouth with the head slightly flexed and the chin tucked well into the neck. If there is difficulty in obtaining a picture in this position because of damage to the lower jaw or severe deformity of the spine, a satisfactory view of the odontoid process can be obtained by X-raying from above downwards, the required area showing quite plainly through the foramen magnum (fig. 1).

Good X-ray photographs are absolutely essential, and as there is frequently deformity,

and always rigidity, some member of the medical staff should be present to supervise movement and positioning when the patient is X-rayed.

When a fracture of the odontoid process without displacement has been diagnosed treatment should consist of complete rest with the neck supported in a neutral position. For this I favour the recumbent position with a small sandbag or hard pillow behind the neck to support without hyperextending. Rotations are prevented by the use of heavy supporting sandbags on each side of the head and a corset or some form of restrainer to the shoulders and thorax to prevent rotations of the body, especially when the patient is asleep. At an early and convenient opportunity, usually two to four weeks after commencement of treatment, the patient is fitted with a carefully moulded leather collar which grips the lower jaw, mastoid and occipital processes and extends well down the front and back of the thorax. A Minerva collar, which gives the most efficient support to the cervical spine, is not necessary in this injury and is at the best an uncomfortable companion.

Fracture of the odontoid process with displacement forward of the atlas.—This injury frequently causes sudden death due to narrowing of the spinal canal and pressure from the displaced atlas on the medulla. In those accidents where the displacement is not severe enough to result in an immediate fatality the possibility of further displacement with fatal results must be remembered, and careful handling of the patient is advisable in the early stages. As a rule reduction takes place quite easily through recumbency associated with some hyperextension, and no manipulative treatment or traction on the head is necessary. There was in the series of patients who had sustained this accident reviewed for the purpose of this paper always some involvement of the great occipital nerve with consequent pain over the back of the head, and in one case well-marked hyperæsthesia of this area. This discomfort rapidly disappears with recumbency, and the prevention of a recurrence of the deformity constitutes the chief difficulty. The early relief from pain and the return of movements tend to make the patient restive and intolerant of hospitalization. The safest and best treatment is recumbency for at least six weeks, followed after this time by a carefully fitting leather doll's collar, which extends well down the thorax and which, by accurate moulding round the occiput, mastoid process and jaw, will hold the neck well supported against all movements. If for any reason prolonged recumbency is not possible and an ambulatory appliance has to be fitted, the full Minerva collar and jacket extending down to the pelvis is safest. It is at its best an uncomfortable support and should at the earliest opportunity, usually in six weeks, be replaced by the less irksome moulded leather collar. The ordinary short Minerva collar takes all its weight on the shoulders and has no place in the treatment of injuries to the cervical spine. The end-results of fractures of the odontoid are extremely satisfactory. Fibrous union of the fracture has been reported but it is not common in my experience, bony union taking place within six months of the date of the accident.

Displacement forwards of the atlas without fracture of the odontoid process.—In this type of injury the transverse ligament is ruptured without damage to the bone. The accident is almost invariably fatal, from pressure of the odontoid process on the medulla oblongata. In those few patients in whom this fatality is avoided the treatment differs in no way from that for a fracture of the odontoid with displacement forwards of the atlas.

Rotary dislocation of the atlanto-axial joint.—This is an extremely rare injury; in my series there was only one example of this condition. There is very little mention made in the literature about it, but Greeley and Coutts have reported isolated instances. According to Greeley reduction was easily obtained under general anæsthesia, and after three weeks' immobilization free use of the cervical spine was permitted ; there was no relapse. In the cases reported by Coutts reduction took place gradually with apparently satisfactory results. The mechanism of the accident is a forced hyper-rotation of the atlas on the axis, the former pivoting round the odontoid process, one articular mass displacing forwards and the other backwards. In the only example in this series and in those reported by Greeley and Coutts the odontoid process was undamaged. A somewhat similar injury may occur with a fracture of the odontoid process, and when this takes place there is in addition to a forward displacement of the atlas on the axis some rotation of the former, usually a unilateral dislocation, the atlas pivoting on one articular process. In this injury there is considerable narrowing of the spinal canal and a fatal result is not uncommon. The isolated example which I have been able to follow up

was four months old in a boy aged 17 years. Reduction took place gradually under gentle traction in recumbency over a period of ten days. In this case, unlike that reported by Greeley, some recurrence of the dislocation took place because of too early freedom, and further treatment was required.

This uncommon but definite clinical entity must not be confused with the so-called atlanto-axial subluxation which has figured so prominently in the literature in recent years. This latter condition is the familiar acute torticollis which commonly occurs with a sudden muscular effort and which is easily corrected by recumbency or by manipulation with or without a general anæsthetic. The arguments in favour of this being a subluxation of the atlanto-axial joint or of one or other of the lower cervical joints are most unconvincing. The majority of supporters of this theory, Stimson and Svenson, Roberts, Brooks, &c., admit that the displacement is frequently not demonstrable on X-ray although occasionally, they say, it can be seen in a stereoscopic view. When present the displacement is rarely any more than can easily be reproduced in a normal spine by rotation of the neck or poor centering of the X-ray tube. My own belief is that the comparatively common acute torticollis which comes on suddenly as a result of muscular effort is entirely a muscular condition and is not in any way caused by minor displacements of the articular processes of the cervical spine ; these joints have a comparatively wide range of movement and must in consequence vary in appearance with the position of the neck and the X-ray tube.

Injuries to the lower five cervical vertebræ.—It is usual to divide these into three types:—(1) Fractures. (2) Dislocation. (3) Fracture dislocation.

(1) *Fractures.*—The two most frequent fractures of the lower five cervical vertebræ are (*a*) a simple compression fracture of the body and (*b*) a fracture, without displacement, of one or both sides of the neural arch. Both types cause very little discomfort, apart from some pain and stiffness, without any deformity demonstrable on clinical examination. Not infrequently, because of the absence of X-rays or poor radiography, the condition is missed in its early stages. When a diagnosis is made it is usual to treat such cases in hyperextension if the injury is a compression fracture of one of the bodies, and in a neutral position if the injury consists of a fracture of the neural arch without displacement. Most authorities favour a Minerva jacket, some recommending a plaster collar, and only a few advise a short period of recumbency between sandbags or with light traction followed by a moulded leather collar until union is firm. There have been a number of these injuries in my series and I have been impressed with the remarkably good results which have followed apparently inadequate treatment and the very much better mental outlook of the patients. For these injuries I would condemn the full Minerva jacket as being far too efficient and causing totally unnecessary discomfort and mental trauma to the patient. In the compression fractures all that is necessary is a short period of recumbency in slight hyperextension followed by a moulded leather collar which should not be kept on too long. Within two months of the accident the patient should be sleeping without support and very soon afterwards should dispense with the support during the day.

Even if there is some collapse of a vertebra, bony buttresses rapidly develop to fix the anterior border to its neighbours, forming an efficient anterior bone graft ; the malalignment of the intervertebral joints and the slight deformity due to wedging of the affected vertebra cause neither disability nor noticeable deformity.

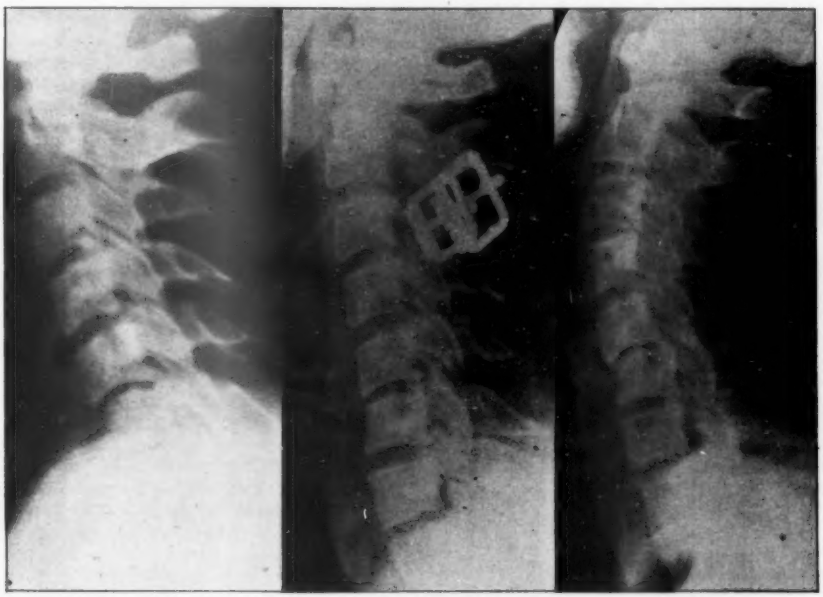
In the fracture of the neural arch similar treatment is advisable because of the difficulty of deciding whether one or both sides are damaged. The immobilization should be even less prolonged and an early return to normal use should be encouraged.

(2) *Dislocation.*—In this injury the inferior articular process of the vertebra slides forward in front of the superior process of the vertebra below. The displacement may be unilateral or bilateral, and the deformity is easily recognizable both clinically and radiologically. According to Langworthy spinal cord symptoms are entirely absent in unilateral dislocations and this has been the experience in the cases reviewed for this paper. Tingling and pain in the upper limb, sometimes associated with temporary paralysis, are, however, comparatively common.

In bilateral dislocations the mortality is high and cord symptoms are found in almost 50% of all cases. As regards treatment, there are two very divergent methods, (*a*) immediate reduction under general anæsthesia, and (*b*) the slow, gradual replacement by traction.

When employing general anæsthesia the method of Walton has been successfully used for over forty years, and the more recent modification of Taylor is a valuable addition to the technique if Walton's method is unsuccessful. The objection put forward to this treatment is the possible danger of sudden death or paraplegia as a result of the manipulation. The probability of such complications is not borne out by the literature and I am of the opinion that, with care, serious complications can be avoided and that it is the method of choice in the recent dislocations and should be tried in the older, unreduced deformities unless the X-ray shows new bone formation which would interfere with the smooth execution of the manœuvre.

The alternative treatment of steady traction has been until recently too frequently a failure. The heavy pull on a halter taking its purchase on the brow or lower jaw becomes unbearable to most patients long before reduction has been accomplished. Within the last six years Crutchfield and others have recommended skeletal traction,



(*a*) 7.9.38. (*b*) 12.9.38. (*c*) 3.1.40.

FIG. 2.—Subluxation of 5th cervical vertebra on 6th, showing the reduction obtained by simple hyperextension followed by recurrence of the deformity and fusion between the affected bodies, causing no symptoms or clinical evidence of deformity.

using special ice tong calipers transfixing the outer table of the vault of the skull. The published results of this form of treatment are impressive and the discomfort to the patient negligible, but I feel that the possibilities of complications as a result of treatment make it not the method of choice, and its use should be reserved for the intractable old dislocation where manipulative reduction has failed or its attempt is considered inadvisable.

After reduction, recurrence may take place if immobilization is not maintained for at least two months. I am in agreement with Simon and others, who state that all dislocations are associated with a fracture of the anterosuperior angle of the body of

the underlying vertebra. Certainly the injury causes damage to the anterior border of the intervertebral disc with consequent fibrosis and collapse of this area, and the late result of reduced dislocations is frequently some wedging of the disc and bony outgrowths interlocking between the two affected vertebræ. The condition is always symptomless and the end-results are most satisfactory (fig. 2).

(3) *Fracture dislocation.*—It is this injury which has the highest percentage of cord symptoms and mortality among all injuries to the cervical spine. C.5 on C.6, or C.6 on C.7 are the commonest sites, the bony injury consisting of a fracture of the neural arch with displacement forwards of the upper affected vertebra; the inferior articular process of the vertebra above dislocates forwards so that the whole cervical spine above the level of the fracture goes forward with the displaced vertebra. As a rule complete dislocation of the articular processes does not occur and replacement can be obtained by gradually increasing hyperextension. If, however, the dislocation is complete, traction

FIG. 3.—Old unreduced fracture dislocation of 4th cervical vertebra on 5th. Now quite symptomless and causing neither deformity, pain, nor loss of movements.

is essential before reduction can be obtained. Because of the increased mobility of the fracture the method of Taylor, which relies on traction and direct manipulation of the fragments, is preferable to the technique of Walton.

In the recent injury reduction is usually easy but the prevention of recurrence is extremely difficult; if even the slightest return of displacement is to be avoided recumbency is essential for three months—even the full Minerva jacket will not prevent minor degrees of displacement. Various additions in the shape of rigging screws and screws

applying direct pressure on the spinous processes have been devised to avoid this tendency to slip, but the plaster headpiece and jacket is uncomfortable enough in itself without the additional appliances.

Fortunately, a certain amount of deformity causes no harm; the end-result of all these injuries, whatever the position of the fragments, is bony fusion between the bodies of the vertebræ, and some displacement causes no harm either in appearance or in function provided there are no nerve-root or cord symptoms (fig. 3).

Tingling, paræsthesia and paresis in the upper limb from pressure on nerve roots are frequent complications and are the main reasons for attempting reduction in the old unreduced deformity. Most of these injuries, even when several months old, improve considerably by simple hyperextension, and it is only on rare occasions, when there has been complete dislocation of articular processes, that other treatment is necessary. It is in this uncommon deformity, in which an old unreduced dislocation is associated with a fracture of the vertebra and nerve-root symptoms are present, that skeletal traction as described by Crutchfield is ideal. In the absence of nerve-root symptoms an attempt at full reduction is not justifiable or necessary in the old unreduced fracture dislocation. Much has been written about delayed cord or nerve-root symptoms, caused by excess of callus and gradually increasing deformity, but if these symptoms are absent when the patient is first seen, then correction of the clinical deformity and efficient immobilization will prevent an increase of deformity and excessive callus formation, but the immobilization must be complete and continue uninterrupted until bony union is solid.

Space does not permit the consideration of the rarer types of injury or displacement of the cervical spine such as fracture of the spinous processes, sometimes termed a clay-shoveller's fracture, nor of the gradual displacement forwards of the atlas on the axis which occasionally takes place in the presence of chronic infection of the throat and nasopharynx.

In following up the late end-results of these injuries the most impressive finding was the remarkable freedom from signs or symptoms in several patients who either refused treatment or had received negligible treatment because of errors in diagnosis. It seemed grossly unfair that the disability period of these patients was considerably shorter than in those who had the recognized treatment commencing within a few hours of the accident. Another noticeable feature in this series was the increase in the neurosis with the increase in the efficiency of the immobilization; a Minerva jacket or closely fitting doll's collar will give a most satisfactory X-ray picture, but it was surprising how frequently it was accompanied by a history of increasing dizziness, vague pains, and other symptoms of neurosis. In every fracture the accepted treatment has frequently to be adjusted to the temperament of the patient, and this is more true in the case of spinal injuries than in any other one type of fracture.

Professor Geoffrey Jefferson: *The common cervical dislocation.*—The greatest incidence of injury coincides with the peaks of mobility in the vertebral column. In the cervical spine this coincides with the 5th and 6th vertebræ. Examination of post-mortem material led me to two firm conclusions: (*a*) that the degree of dislocation depended on the severity of the tearing of the intervertebral disc (which is contingent on the degree of the violence and the biological state of the disc) and (*b*) that the stability of the dislocation is due either to locking of the fractured tips of the articular processes or to the zygapophyses of the upper vertebra so far overriding the lower that they cannot return. Reduction is easiest when there is grave injury to the cord; the disc is then usually severely torn and the vertebræ mobile on one another. The lesser grades are often most difficult to reduce. We shall have to consider the methods of reduction and to inquire whether adequate treatment has even then been provided. The evidence that follows raises doubts and suggests that continued traction is as necessary as reduction. In cervical dislocations the injury to the disc is often severe enough to cause its disintegration, with backward protrusion (or retropulsion) into the spinal canal. It is clear that the disc debris consists of more than nucleus pulposus alone; the disorganized nucleus and annulus fibrosus form a formidable mass pressing on the anterior surface of the cord. Sometimes disc substance can be seen to extend for a considerable vertical extent. I have long been convinced that the popular belief that the spinal cord is damaged by the dislocated neural arches, i.e. that the pressure is chiefly on the dorsal surface of the cord, should be revised. Very often an equally

serious compression occurs on the ventral surface of the cord in the form of this retropulsed disc material, a compression not completely relieved by mere reduction of the dislocation. The disc debris is likely to continue its pressure however perfectly realignment is achieved; it can only be given an opportunity to withdraw if traction is applied and maintained. If the normal disc height can be reproduced by this means, it seems likely that some at least of the disc substance may find its way back into the intervertebral space ; even if that does not happen, traction should straighten out the knuckle pressing on the cord.

The nature of the cord injury.—Neural injury consists of (*a*) root damage, (*b*) cord contusion. Root injuries are the rule whether the cord is involved or not; pain streaming on to the shoulders and down the outer sides of the arms is almost invariably present. The cord injury, which we too often picture as an almost linear band across the cord, a few millimetres wide, is usually from 3 to 5 cm. in depth. Post-traumatic œdema has the power to increase further still the damaged area, so that the clinical level may rise and bear a puzzling relationship to the X-ray evidence of the level of dislocation. The blood supply of the spinal cord has recently been carefully re-studied, and as a result teaching must be modified. It is clear that the vascular supply is far from being the schematized affair that appears in textbooks, that the entering segmental arteries are very variable in size and importance, that large vessels are scarce. It follows that an artery may be damaged which supplies several segments above it and thus produce anomalies in clinical levels. As for the nature of the injury, it is often assumed that the central grey matter of the spinal cord is so richly supplied with blood that a squeeze will lead to a severe central hæmorrhage. I have previously raised doubts as to the validity of this belief because I have found the spinal cords of those dead from cervical fracture to be remarkably free from gross hæmorrhage. They show (1) a gross distortion of internal pattern with fissuring of the cord substance due to the unequal resistances of the components of the neural tissues, long and short tracts, grey columns, blood-vessels, and the many prolongations from the pia which make up its named septa and its many short unnamed bands. (2) The central mass of the cord is not the area most damaged. (3) The subpial, cortical region is often torn radially by the drag of pial penetrating fibres. The pial envelope itself is torn across only in the severest lacerations. It cannot be contended that the vessels are never ruptured and that hæmatomyelia is never seen, but it can truthfully be said that intraspinal bleeding is less common and less immediate a cause of death than is non-hæmorrhagic contusion, the fracture of axons, cellular disruption, and œdema.

The neurological signs presented by any case are, of course, those of physiological block, of arrest of impulses in either direction, due either to contusion or to real destruction. Sometimes the block is complete, sometimes incomplete. We have learned from experience that when both sensation and motor power have been totally lost below the level of a cervical lesion death is almost certain to follow. I have seen no case with a total sensory loss recover ; on the other hand, I have seen many with a total motor palsy do so, for the following reasons :—

Loss of motor power.—Liddell has shown that the central excitatory state of anterior horn cells in the motoneurone pool requires "boosting" by a barrage of impulses which normally fall upon it from many sources (from neighbouring cells, from anterior horn cells at a distance in the cord, from sensory impulses from the neighbouring somites in their totality of depth, from all descending and ascending tracts which form synapses with it). The number of fibre connexions made with a single anterior horn cell supplying a muscle to a lower limb is not known but it can probably be counted in the hundreds. Failure to move the lower limbs is no evidence, therefore, that the pyramidal tracts are destroyed, as we well know from experience with the paraplegias of Pott's disease, of removable spinal tumours, and indeed of injury itself. We can, however, be more certain of recovery if a flicker of voluntary movement in one or both legs remains after the accident, and if the tendon reflexes can still be elicited.

Sensory loss.—Loss of power, or lack of power, is not, then, certain evidence that the pyramidal tracts themselves have been severed. We turn next to sensory tests to complete the estimation of the extent of the conduction block. Sensation is normally a much more complex affair than appears; there is a vast difference between normal sensation as we use it in ourselves and sensation as that composite of sub-varieties into which ingenuity has dissected it. Sensation, to ourselves, has to do with the total nature of the object felt

and is greatly dependant on movement. Indeed all discrimination, all measurement (which is greatly what we use, so to say, sensation for) is a simultaneous compound of movement, joint and muscle sense, cutaneous sense, all concerned with the total nature of the object felt. We apply sensory tests of many kinds; in these we supply the necessary movement, even in so slight a thing as by a touch, the patient being inert. Sensation, then, is normally something which is active and is indissolubly bound with motor action; in our testing we investigate only bits of sensation under passive conditions rarely experienced in ordinary life. These things are mentioned because of the difficulty that most honest people have in producing accurate charts of sensory loss; they are never easy to make unless there is deep anæsthesia. When in a cord injury there is sharply limited and profound sensory loss up to the estimated level of the lesion the prognosis is bad. The question arises, why should it be so ? The answer, as I see it, is that sensation in the spinal cord is for the most part a matter of plain conduction along tracts, without the use of those synaptic connexions which are characteristic of the motor apparatus. The exception is the transmission of pain and temperature sense, and it is not without significance that these modalities are sometimes lost without an equal interference with other kinds of sensation. Synaptic block becomes, therefore, a possible explanation for this sensory dissociation. An alternative may lie in the fact that the spinothalamic tracts lie close beneath the surface of the anterolateral columns, and injury is commonly cortical; large parts of the posterior columns may escape injury (as the histology of damaged cords has shown). To sum up : I should expect a case of pure spinal shock to exhibit diminished or lost power of movement, numbness to pin-prick, but with other kinds of sensation largely retained.

Prognosis

We all feel the need of some sign by which we could say with certainty that such and such an individual would do well, such another badly. I do not believe that any single sign exists and can do no more than make a generalization : that loss of motor power is a less grave sign than loss of sensation, that those patients eventually do best who have primarily only a partial sensory loss (often tending to the Brown-Séquard type but practically never fully reproducing his syndrome) with some power of movement, however slight, retained. A more detailed discussion seems to me to be likely to be no more informative. It is, of course, fortunate that a large proportion of cervical injuries are not complicated by damage to the spinal cord. If a late compression occurs in a reduced dislocation the cause is unlikely to be on the dorsal surface of the cord. The disc may then be the causal agent, but I have not yet seen such a case ; they are rare.

Treatment

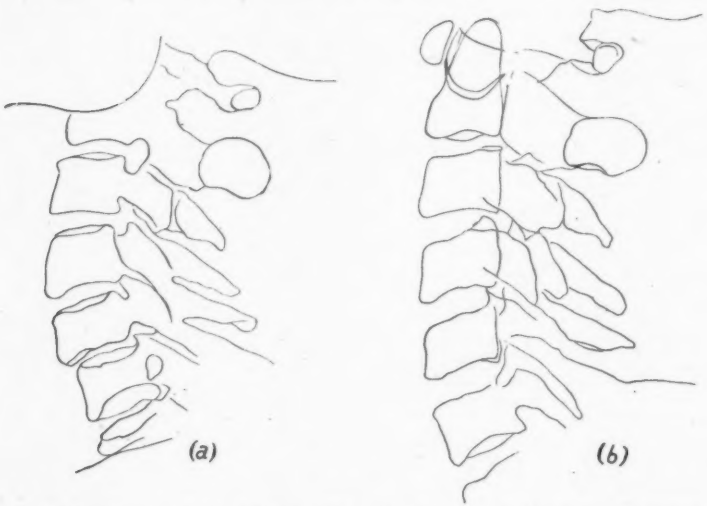
Reduction of a dislocation can be effected in a number of ways: A. Immediately by forcible traction, usually under an anæsthetic. B. Gradually, by (1) a sling under the chin and an inclined plane; (2) Crile's pneumatic head band; (3) by some method of skeletal traction.

Generalizations of this kind have the advantage that they tell us in brief the methods which are applicable, and unsatisfactory in that they do not tell us what we ought to do with any given patient. If we can agree to adopt some method and standardize it, we shall then at a later date be able to evaluate that method.

A. *Rapid reduction.*—This method was introduced by A. S. Taylor of New York in 1924. A chin strap is fixed to encircle the patient's chin and the suboccipital region and as much force as may be desired applied by a series of pulleys. Although Taylor claimed successes I was never convinced that complete reduction had been achieved, in either Taylor's cases or my own. I used it four times; twice a partial, and as events proved, a satisfactory reduction was obtained, once no change could be effected (dislocation between C.2 and C.3) and once further cord damage was, I fear, inflicted, with the eventual death of the patient. This last case caused me to abandon the method. The danger, as I see it, lies in the fact that, when the cervical spine is forcibly pulled upon, the surgeon has little control over the direction which the bone-ends take at the moment when they are disengaged. Furthermore, a neck strongly stretched is difficult to manipulate, for its component parts are no longer elastic. I have, as the result of my experience, no belief in the efficiency nor in the safety of this method. Nor does it solve the problem of the disc lesion.

B. *Gradual reduction.*—The first method, reduction by a sling under the chin and occiput with the application of mild but continuous traction either by weights or by an inclined plane (and in either case the head of the patient must be raised) is a method which may succeed. If it were the only alternative to the one just discussed I should strongly support it. I believe, however, that it is an intolerable one for the patient and should be superseded. This is equally true of the Crile pneumatic headband which requires such a degree of inflation, if it is to grip, as must endanger the blood supply of the scalp. Necrosis has followed its use and it will be abandoned, though perhaps with regret.

This brings us to skeletal traction either by calipers or by wire.



(*a*) Dislocation, 5th on 6th cervical. (*b*) The same after three weeks' traction. Note recovery of disc height.
(Tracings from radiographs.)

Caliper traction.—Calipers were first introduced by Coleman, McKenzie and Crutchfield. Some forms have the disadvantage that it is not possible to turn the patient for nursing purposes, an objection not shared by the wire traction method of Turner and Cone. The radiographs from a patient illustrate well the advantages of the method, on this occasion with the Blackburn tractors. I owe these to my colleague, Professor Platt (figs. *a* and *b*). It will be observed that, not only has the dislocation been satisfactorily reduced, but that the disc spaces are increased by the traction, and no more so at the point of injury than elsewhere. This is an important happening, because it seems likely to solve the problem of the retropulsed disc. It is of especial value in cases with neural damage; the anterior pressure factor will be more likely to be relieved if the traction is maintained for three weeks or more, a time that should be sufficient for a considerable remodelling of the intervertebral disc. When there is no neural damage there is not the same necessity for lengthy periods of traction. It should suffice if it were kept up for a week or so, i.e. until such time as the natural tendency for recurrence of the dislocation is past. The advantage of being able to apply a collar whilst the traction is maintained is clear.

Wire traction.—If no caliper is available traction can be applied by the method of Turner and Cone, stainless steel wire being carried extradurally between two burr holes on each side in the skull above the ear. The wire can safely be left-in place for many days.

Section of Laryngology

President—T. B. Layton, D.S.O., M.S.

[*May* 3, 1940]

DISCUSSION ON THE POSITION OF RADIOTHERAPY IN THE TREATMENT OF MALIGNANT DISEASE OF THE UPPER RESPIRATORY AND ALIMENTARY TRACTS, EXCLUDING THE TONGUE AND ŒSOPHAGUS

The President said that when a new therapeutic measure was introduced, three things might happen. In the first place, it might lead to an evolution of previous methods already in use. Of the two great advances in surgery in the last century the development of general anæsthesia came under that head. Secondly, it might necessitate a complete and entire reconstruction of the whole of the approach to a surgical problem. That was what happened when Lister introduced his antiseptic method. Thirdly, it might be one of those things which came in, were tried, and were weighed in the balance and found wanting.

Was radiotherapy to be an accessory in the service of the surgical principles already laid down? Or would it be necessary entirely to revise them, and to look upon it as a primary method of attack, with operative surgery as a secondary line? Or, again, was it going to pass in the same way as the injection of Coley's fluid and other methods?

G. F. Stebbing: During 1938 there were admitted to Lambeth Hospital 1,162 cases of malignant disease of which 58 or 5% were carcinoma originating in the pharynx (including tonsil) and larynx (including epiglottis). I have put these together as they are the subject of to-day's discussion but it is difficult to consider them as a single group. In this region of the body many different types of tumour are found; the possible primary sites are numerous and there are so many different methods of evolution that a classification which is of any use at all is difficult and intricate.

During the ten years 1929-38, 392 cases of carcinoma of the pharynx and larynx were admitted to Lambeth Hospital under my care. It is my fate to deal with a very large number of patients whose disease is so extensive or whose general condition is so feeble that little can be done to help. Many, before coming to me, have had surgical or radiotherapeutic treatment elsewhere. Radical surgical operation was not used in Lambeth on any of these patients. Prior to 1929 I had been accustomed to excise, in suitable patients, operable growths in some of these sites but by that year I had learnt that these were just the cases in which I could get as sure a result by radiation without the disability inseparable from radical surgery. The proportion of operable growths among the 392 patients mentioned above, by whatever standard operability is judged, was very low indeed.

In order to produce a classification of any value it is necessary to divide the 392 cases into six groups according to the primary site—tonsil, pharynx, pyriform fossa, epiglottis, larynx and post-cricoid, and each of these groups must be subdivided according to (*a*) the extent of the primary disease, (*b*) the invasion of neighbouring structures and, if so, which, (*c*) the invasion of regional lymph nodes, (*d*) more distant metastases. Each of these subdivisions has to be further divided according to whether the disease occurs in a patient whose general condition permits of an attempt at radical treatment. By the time that is done we find ourselves with about fifty different groups, and we have not yet taken into consideration the different pathological types that occur in each of these situations. In each of these the growth may be proliferative or infiltrating. If our classification is to help us in either treatment or prognosis the group must be subdivided under these headings. By the time the 392 patients have been grouped, each subdivision is so small

as to be statistically uninteresting. If we make the groups larger by adding many of them together we only disguise and do not get rid of the statistical errors.

Of my 392 patients, 190 were in such an advanced stage of disease and so feeble that only palliative treatment could be given and as these 190 are distributed through all the groups no reliable conclusion can be drawn from statistical analysis. I will content myself with reporting that out of 306 treated before the end of 1936, 21 were alive and free from symptoms three years later.

In 1931 Coutard published an account of 212 cases of carcinoma of pharynx and larynx, of whom 20% were alive five years later, and the method that he employed has been repeated in many places and, with some modification, is used now by the majority of radiotherapists. It consists of focusing on the growth a narrow beam of X-rays of low intensity for a certain time each day for three to six weeks or more, controlling accurately the dose of radiation delivered to the tumour so as to produce the maximum reaction just at the time that the full dose has been given. Stated in that way the problem does not seem a difficult one but in practice the difficulties are so great that there are few clinics in this country in which it can be efficiently carried out.

Because the lesions are at the upper end of both respiratory and alimentary tracts there is a grave danger to life if the reactions produced are excessive and unnecessarily widely distributed. It is therefore important to make an accurate diagnosis of the extent of the lesion so that only that tissue which must be regarded as infiltrated shall be treated. In most cases the regional lymph nodes are affected by the growth and they must be included in the radiation. To spare the healthy structures of the neck the growth must be attacked from as many sides as possible, and in directing the beam through each of the fields the head must be turned into a position that brings the growth as near the skin as possible, and the applicator that limits the beam must be used to push out of the way any structures that can be so pushed out of the radiation. In doing this it is very easy to move some of the growth out of the beam, but if this is avoided and we succeed in aiming satisfactorily we have still to remember that a slight movement on the part of the patient, a movement that cannot be controlled by head clamp or mechanical contrivances, can in a second undo all our work and make us start over again. Most of the failures that we see in cases in which we might reasonably have expected good results are due to this failure to keep the whole of the growth in the beam the whole of the time, and I shall refer to this error by the title of "geographical miss".

Our next problem is to measure accurately the dose of radiation, and it is our custom to record the tumour dose that is delivered at each daily session. It is not difficult to calculate the amount of radiation delivered at any point, provided we know its depth below the surface and the nature of the structures by which it is surrounded. But serious errors do arise owing to the variation in the depth of the tumour caused by small movements of the head, and by the presence around the growth of the air spaces of the pharynx and larynx. I have spoken as if the tumour dose were one figure, but when we are using many crossed narrow beams to irradiate a given area the volume that receives a uniform radiation is a small one, and the tumour dose must be calculated at several points if we are to make sure that that volume of high uniform irradiation contains the whole of the tissue that we have decided to regard as infiltrated. An attempt has been made to carry out this method of measurement in many places but was most successfully achieved by the Radium Beam Therapy Research—the interruption in the work of which must be regarded as one of the tragedies of the war. To some extent the distribution of the reaction produced will tell us whether our radiation has really reached the points it was intended to reach, when the parts can be seen by direct or indirect examination. But if reliance is placed on the appearance and degree of the reaction valuable time will be lost and less favourable results produced. Measurements indicating the dosage of radiation have little meaning unless they are accompanied by a full description of the method of treatment, but generally speaking it may be said that for the lesions under discussion about 4,500 r should be delivered in twenty days, the dose increasing if, owing to the reaction, it has to be spread over a longer time.

The radiosensitivity of the growths in this part of the body varies very greatly. The growths range from lympho-epitheliomata which will generally entirely disappear with 3,000 r given in twenty days to hard, warty localized growths which will disappear only when the radiation is pushed to the extreme limit of tolerance of the normal tissues

and to scirrhous carcinomata for which nothing but caustic doses of radiation are any good. It has been our custom to treat all these cases in the first instance by X-ray beams. But in many of the cases, owing to the extent of the primary disease and the spread of metastases the beams employed have to be large instead of narrow. In such cases it is not possible to produce as satisfactory a reaction because it would be so widely spread as to produce fatal complications. It has been found, however, that after the reaction has passed off, the growth has been reduced to a small compact lesion which can be given a further dose of radiation, either by a surface application of radium, an interstitial implantation of radium needles, or by contact X-ray therapy. In using this local radiation it is just as necessary as in using the X-ray beam that the radiation should be evenly distributed over the whole volume to be treated, and the quantity of radiation measured. If operations of access are necessary they should be planned to avoid any tissue that may possibly be infiltrated and should pass if possible through tissues that have not received a full dose of radiation. We have now come to regard this combination of X-ray beam followed by a local radiation as the method of choice in the treatment of certain of the lesions under discussion, for example that common carcinoma which starts clinically as a fissure between the tonsil and the tongue, and which so often only presents itself to the surgeon because of a hard fixed gland in the neck. This carcinoma is generally widely spread in the tonsil, fauces, floor of mouth, tongue and lateral pharyngeal wall, and its radiosensitivity varies considerably. A small number of them disappear rapidly when treated by X-ray beams alone. As a rule, the X-radiation is delivered through five fields, three on the side of the disease and two from the opposite side of the neck, each beam having a cross section of about 50 sq. cm. An average of 200 r a day can be delivered to the tumour through these fields until the necessary tumour dose of 4,500 r in twenty-one days has been delivered. If the glands are much enlarged it may be necessary to add some extra beams to build up the dose in that part of infiltrated tissues.

The reaction reaches its height at or soon after the end of the X-radiation and will take about three weeks to pass off. It is generally possible to tell at that time whether further irradiation is needed. The fissure will in any case be healed but the mobility of the parts and the character of the œdema are the points on which a decision will have to be made. It is important to recognize that in those cases—and they form a fair proportion—in which it is doubtful at this time whether a large enough dose has been given, further irradition should immediately be used instead of waiting for further signs. The further radiation in these cases is given by an interstitial needling, radium needles of not less than 3 cm. of active length and containing 1 mgm. to each cm. should be placed in the base of the tongue and in the lateral wall of the pharynx and the base of the fauces, at right angles to the surface so as to form a cylinder in which the whole of the indurated area is enclosed. If the cylinder is not more than 2·5 cm. in diameter there is no need to put needles through the indurated area itself, and it is not necessary as a rule to stitch the needles in. If they are pushed in so that their heads lie level with the surface they will retain their position for the 90—120 hours which is all that is needed to deliver the further radiation required. In inserting these needles the object is to keep them parallel to one another and forming a cylinder round the lesion, and it is always a good plan to have an X-ray photograph taken of the needles in position. Such a photograph prevents anyone from thinking that he can place radium needles where he wishes.

It is a misfortune that the common growths which originate in the pyriform fossa cannot be treated in this same way. They are a type of growth which one would expect to give good results by it, and many of them respond very favourably in the first instance to treatment by X-radiation. The difficulty, however, of giving the added local X-radiation is very great, and although I have made attempts at radium implants from the outside, and radium needling and implanting of seeds from the inside, my efforts in that direction have not been successful. There is a field for research, which so far as I know has not yet been touched, in treating growths of the pyriform fossa by X-radiation followed by contact therapy.

The treatment of intra-laryngeal growths by means of radiation was fully discussed by Douglas Quick (1937) before the American Radium Society, when he reviewed the results that had been obtained both by surgery and radiation. Growth occurring on the vocal

cords, limited to one of them, can be removed by laryngofissure, leaving the patient with little disability. But there are many cases on record in which such growths have been treated by radiation, leaving the patient with no disability. In my 392 cases there were only two of this type who were well enough to undergo any treatment, and they were both treated by X-radiation and have both remained symptom-free, one for nine years and one for four years. I have seen several of these cases in which insufficient radiation has been given, and operative removal is, I believe, the only treatment since radiation cannot be repeated.

It is true of radiotherapy as it is of surgery that the earlier the patient comes under treatment the better the result that can be expected. But it is also true of radiotherapy that surprising results are sometimes obtained with patients whose disease is very advanced. Out of 58 cases of carcinoma of the pharynx in which there were large and infiltrated glands of both sides of the neck, five were alive and free from symptoms of disease three years after completion of treatment, and in this lesion that probably means that they will not get any further recurrence.

Among the special difficulties and dangers of radiotherapy is the danger to every patient during the stage of reaction. This is comparable with the danger to the patient in the post-operative stage of surgical excision. If the reaction is carefully controlled and the patient is well treated, the risk is not a great one, but it is a formidable problem in the old and feeble patients who are so prominent a feature of my clinic. The danger of radionecrosis following excessive or badly directed radiation has, in the past, caused much trouble, but not as much as many people believe. It is true that radiotherapy diminishes the resistance of tissues that receive a full dose, and if a septic infection occurs in those tissues within a few months of radiotherapy troublesome sepsis may occur and healing may be prolonged. But radionecrosis is rare now in clinics where doses are properly measured and patients carefully observed.

There is another difficulty of radiation which is less easy to explain. We have seen a number of patients, particularly those in more feeble general health, who have stood satisfactorily the whole course of radiotherapy, whose growth has entirely disappeared, but who have died of a low form of pneumonia within a few weeks of the end of their treatment. I think it is possible that the irradiation in these cases has deprived the patient of the immunity-producing mechanism that is normally in his throat, and that he thus succumbs to an infection which in a normal person would be nothing more than a transient coryza. This lowered resistance to infection is a danger that should never be forgotten, and in preparing a patient for radiotherapy it is just as essential to clean up all possible sources of infection, such as septic teeth, as it is in preparation for surgical excision. Anæmia and malnutrition should also be corrected.

We are accustomed to gauge our success by the number of patients surviving at the end of some years from the time we have treated them, and if we were to judge by that standard only I should have to regard my work as a failure. Of the 392 patients only 21 were alive at the end of three years. But of the cases which were treated and who ultimately died of their carcinoma, the large majority were rendered symptom-free for many months and sometimes more than a year before they died from metastases in distant parts of the body. In a large number of these patients the treatment was successful in relieving the symptoms that the patient had when he first presented himself, in giving him a period of apparent health and allowing his life to end by an easy method. I am, however, bound to admit that there were among those 392 patients some who, although they had this period of temporary respite, ended their days in a very distressing condition due to infiltration of the growth in the thoracic inlet and supraclavicular region. In most of these cases the initial mistake was made of underestimating the extent of the growth. No treatment was undertaken in this region until it was too late, and my only comfort in thinking of these patients is that they were better off than many that I have seen who had never had radiation, and who were in the same condition with the added disability of their primary lesion still in existence.

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Lionel Colledge: For several years I have felt that radiotherapy applied in the region of the pharynx and larynx has failed to justify itself, and that a heavy load of responsibility rests upon those who refuse to abandon a method which is seldom successful and has been the cause of much suffering and of the loss of many lives which might have been saved by surgery.

I am only too well aware of the limitations of surgery for these cases, and that many present themselves in an inoperable condition. I have published some results elsewhere,[1] but the tables given here indicate what at present may be expected from surgery. These tables refer to 153 cases submitted to operation between 1920 and 1935, so that at least five years have elapsed since the last operation. Among the 76 remaining well there are 34 cases which have passed the ten-year period without recurrence, 27 in the intrinsic group and 7 in the extrinsic group.

INTRINSIC CASES

	No.	Died	Recurrence or untraced	Known to remain well
Laryngofissure or partial laryngectomy	23	2	3	18
Total laryngectomy	75	14	18	43

EXTRINSIC CASES (PHARYNGEAL)

	No.	Died	Recurrence or untraced	Known to remain well
Pharyngotomy	39	9	18	12
Pharyngo-laryngectomy	16	3	10	3

The results are not so good as might be desired but they at least show some return for the labour expended, and I have always felt that if some of the conveniences and cash which are lavished upon radiotherapy had been available more might have been accomplished. My pessimism concerning radiotherapy is based partly upon the results of radiotherapy shown in this table published by the Medical Research Council.

CANCER OF THE MOUTH, NASOPHARYNX, LARYNX AND OESOPHAGUS TREATED BY RADIOTHERAPY

	Larynx		Pharynx, nasopharynx and pharyngeal wall	
Year	Living	Dead	Living	Dead
1925	0	5	0	5
1926	0	7	0	4
1927	0	7	0	1
1928	0	9	0	3
1929	0	7	0	9
1930	1	31	2	24
1931	0	24	2	33
1932	1	24	2	24
1933	0	23	1	43
1934	6	27	2	27
1935	5	49	3	31
1936	9	37	4	13
1937	14	42	10	21
Total	36	292	26	238

Medical Research Council Special Report Series, No. 236. "Medical Uses of Radium. Summary of Reports from Research Centres for 1938" (Table 19). Published by permission of the Controller, H.M. Stationery Office.

If the ten-year period 1925-1934 be taken, there are very few five-year results—eight out of 172 of cancer of the larynx and no ten-year results. To obtain these figures the results in the table subsequent to 1934 must be discarded. It has become the customary formula when announcing the results of radiotherapy and the proposed changes of technique which are to follow shortly, to say that the results have been encouraging.

[1] *Brit. M. J.*, July 23, 1938 (ii), 167.

I fail to see what encouragement these results offer, if the usual standard adopted by surgeons of a five-year period after treatment is adopted. I am well aware that the primary growth often disappears rapidly under radiotherapy, for I have seen it do so often myself, thus encouraging premature publication of results.

This reaction of new growths to radiation shows that the whole basis of radiotherapy is built on sand because recurrence takes place, except in rare cases, locally and unless the original cancer-bearing area is excised recurrence is almost inevitable.

I referred before to the question of operability, which makes strict comparison between surgical and radiological treatment impossible, because surgical cases must by definition be operable whereas radiological cases may or may not be operable.

In reporting the results of radiotherapy it is usually stated that most of the cases were inoperable, but operability is a matter for individual judgment. A patient was sent to me from India with a post-cricoid carcinoma high up behind the larynx and a mass of glands on the left side of the neck. Before accepting my recommendation for a pharyngolaryngectomy he sought another opinion from a source with a strong bias towards radiotherapy and profoundly conversant with its practice. The opinion which he obtained was that his case was inoperable and was even so advanced that no hope of benefit by radiotherapy could be offered. This patient is now, after a little more than two years since the operation, quite well and free from any sign of recurrence, and the case makes me think that many others are declared to be inoperable and hurried off to radiological destruction without sufficient consideration of what could be done for them. Another reason for this opinion is that a large proportion of the cases which now reach me have already been treated by radiotherapy. Many of them are failures by this treatment but still operable. Also I know that many patients to whom I have recommended operation have preferred to seek the illusory benefits of radiotherapy and this again makes me think that the proportion of inoperable cases in radiological statistics is not so high as is stated. This is of importance because it is the early and operable cases which derive benefit, even if only transient, from radiotherapy. In the more advanced and inoperable cases the condition is aggravated by the treatment, and the general poisoning proves rapidly fatal. Chevalier Jackson has drawn attention to this in his recently published book on "Cancer of the Larynx", and it places serious limitations on the use of radiotherapy even as a palliative form of treatment.[2]

The value of radiotherapy can be settled only by statistics and I have endeavoured to present my few figures in the simplest possible form, though even so a statistician would probably find fallacies in them.

Although there are occasions when the employment of radiotherapy is justifiable, such as in cases of malignant disease in the nasopharynx, it has failed to justify itself as a routine treatment for pharyngeal carcinoma, still less for laryngeal carcinoma, and a great deal more might be done by careful surgery of these regions.

Walter Howarth: In estimating the relative value of radiotherapy and surgery, it is essential that we should only compare the best with the best. Radiotherapy is a comparatively new and, until recently, a changing method, and unfortunate results may have followed from its use in unskilful and timid hands; whilst surgical intervention in some hands has not always been as skilful and as thorough as it might have been.

For a great number of years I have had considerable experience of both methods, and I should like to say something about them in intrinsic cancer of the larynx, and in epilaryngeal or extrinsic cancer of the larynx.

Intrinsic cancer in which the growth is small and confined to the free edge of the vocal cord.

What can the surgeon do? He can cure the patient in 80% of cases and leave him with a good and useful voice. There are a variety of statistics to prove this.

My own series of more than 25 cases treated by laryngofissure without a tracheotomy (which I regard as neither necessary nor desirable) conforms to these figures, and all have passed the five-year period.

What can radiotherapy do? I do not know, and the radiotherapist does not know, because he is not allowed to see these early cases.

To discuss the question of treatment of these cases by a combination of surgery and

[2] Chevalier Jackson and Chevalier L. Jackson, "Cancer of the Larynx", p. 49. W. B. Saunders Co. Philadelphia, 1939.

radiotherapy such as that introduced by Ledoux and popularized in this country by Harmer is to confuse the real issue, and though I have had some successful cases by implantation of a palisade of radium needles after resection of the thyroid ala, I have also had and seen disastrous results, so that I am sure that pure surgery is to be preferred for these cases.

Advanced cases of intrinsic carcinoma involving the arytenoid or ventricular band, which are beyond laryngofissure.

What can the surgeon do? He can, by total laryngectomy, remove the growth and cure the patient in say 70% of cases, but at what a cost? Look at it how you will, it is a terribly mutilating operation and though I have certainly three cases that have passed the ten-year limit alive and well, I have not removed a larynx for some years and am inclining to the view that it is no longer a justifiable operation.

What can the radiotherapist do? He *is* allowed to see these cases. The report of the Radium Beam Therapy Research,[3] though the material is small and the period of cure as yet under five years, points the way as to what can be achieved; and Case D.35, illustrated in this report, is most illuminating, as the growth has completely disappeared and the larynx is restored to normal. What the radium bomb can do I believe that deep X-rays can also perform, and the outlook in these cases for the radiotherapist is most hopeful. I mention the Radium Beam Research because several cases from my clinic were treated there.

Epilaryngeal cancer.—In 1913, Mr. Trotter brought out his epoch-making method of approach by lateral transthyroid pharyngotomy, and his method of excision of tumours in favourable cases. I listened to his lectures and, in that year, began my own series of cases by his method. In my hands over a period of twenty years they have proved most disappointing. When in 1931 I was President of this Section, I got Mr. Trotter and Professor von Eicken to open a discussion on this very subject and I was anxious to get together a group of illustrative surgical cases, but, though I tried very hard, it was very difficult indeed to get a series that had passed the five-year period. My own successful cases were well below 10%, and though Mr. Trotter has given in various papers and in conversation reports of various successful cases, I do not know of any complete series of statistics of his cases so that I do not know how favourable they are. Mr. Colledge has given some figures which are difficult to understand, but I gather that his series only includes seven cases of cure in epilaryngeal cancer. Can this be considered at all satisfactory? I think not.

What can the radiotherapist do? In 1931, when this subject was last before the Section, Coutard in Paris, Holthusen in Hamburg, and Schinz in Zürich were perfecting their methods, and I was very impressed on seeing their cases and results in Zürich. In this country, Mr. Stebbing has employed his modification of these methods for many years, and with the vast amount of material at his disposal and the highly trained team under his direction has obtained results that are sometimes astonishing.

I have seen many of his cases before and after treatment, and can only say that the results are most remarkable. Many of his cases are not early ones, but are cases with massive infiltrating growths in the pyriform fossa, deep pharynx and base of tongue, with a huge fixed mass of glands in the neck—cases beyond the wildest hope of surgical intervention. Under Mr. Stebbings' treatment, these growths can disappear almost magically and the tissues resume a normal appearance. Surgery has nothing to place beside this.

Sir Alfred Webb-Johnson, who was called upon to speak as a general surgeon, said that he was not expecting to take part in the discussion; he had come to learn. He did think, however, that they were at grips with this problem in many regions of the body. In some cases where radical surgical operations entailed a heavy primary mortality, and in others in which there was serious mutilation, surgeons would welcome an alternative method of treatment. He thought there was no doubt that in some regions of the body radiotherapy had completely justified itself. It had done so, for example, in cancer of the uterine cervix and in many cases of cancer of the mouth and of the skin. When it came to regions like the larynx and pharynx, as regards general advice to patients, practitioners would have to consider very seriously whether they recommend the specialist who favoured radiotherapy, or the one who favoured operation.

[3] Medical Research Council, Sp. Rep. Ser. No. 231.

Satisfactory results by radical operation had been obtained by surgeons of superlative ability, and even their results were sometimes equalled in radiotherapy centres of the highest class. That was an important aspect to keep in mind, for in radiotherapy as well as in surgery, it was the man behind the machine who counted.

He found it more and more difficult to arrive at the truth by a study of statistics. It was practically impossible to get comparable groups of cases. Mr. Colledge's cases were selected ones, all assessed as operable, while the great majority of the cases which Mr. Stebbing had mentioned were cases which even the most expert surgeon would not attempt to deal with by radical operation. The fact that Mr. Stebbing had got even some patients alive at the end of five years should encourage them to give every facility to those who were carrying out this work. By "every facility" he meant that those who controlled radiological clinics should have at their disposal all the radiological means which might be desirable for the treatment of their patients. There were cases where they wished to use X-rays or the radium beam, or to implant radium, or apply a radium mould. The work could only be done properly if they could use the method best suited to an individual case.

The radiologist who was not a competent surgeon himself, or who had not got the constant collaboration of such a surgeon or specialist surgeon, was not in a position to give patients the attention which their condition required. The help of one or other colleague was constantly needed, not only in deciding whether the primary treatment of a case was to be by surgery or by radiotherapy, or by a combination of the two, but also in deciding whether surgical or radiation treatment should be used in case of initial failure, or in case of recurrence. The treatment of cancer in many regions was essentially team work and did not belong exclusively either to the surgeon or to the radiologist. The team should consist of surgeon, or specialist surgeon, radiologist, pathologist, and physicist.

C. A. Scott Ridout said that after much experience during the last fifteen to twenty years, for certain cases he would advise surgery every time, provided it did not mean too great mutilation and in such cases he regarded radiotherapy as the handmaiden of surgery. In other cases he agreed with Mr. Howarth concerning extensive laryngectomies and the mutilation they entailed, but he was also in agreement with Mr. Colledge as to some of the terrible results of radiotherapy. He remembered one case of a middle-aged American in whom he discovered a carcinoma of the pyriform fossa. He saw him with Sir StClair Thomson, and a biopsy showed malignancy. The man was unable to stay in England, so he sent him to Dr. Chevalier Jackson in the States, who referred him to a radiotherapist. He himself saw this patient later in America after treatment. The growth had disappeared, but the man had been "knocked out" by the treatment, and he was then only just recovering from the secondary effects. Within six weeks he died from some intercurrent trouble which seemed to have been hastened on by the treatment he had received. He recalled another case treated by radium in which the growth disappeared from the floor of the mouth as by magic, but it recurred, and the state of that man was much worse than before and much worse than it would have been had diathermy excision been practised. Taking these cases and the results one got by diathermy excision or surgery plus radiation, he still said that it was necessary to keep an open mind.

Professor F. R. Nager (Zürich) said he was very gratified to hear the ideas of his British colleagues. In Zürich they had an excellent radiologist, Professor Schinz, and he was so enterprising that their experience of operations had become more and more rare. From this point of view he shared the opinion of Sir Alfred Webb-Johnson that there was a certain danger in losing experience and the art of performing operations. On the other hand, the question of mutilation by operation seemed to be very important. He remembered two cases of patients on whom laryngectomy was carried out and unfortunate psychological results in the form of melancholia followed. The effect of the mutilation was a factor to be taken into consideration. In Paris, 1924, Tapia showed his cases, and all were impressed by his good results. But in total laryngectomy a great deal depended on the patient himself and whether he could stand the mutilation. If one were not quite sure about this, a less drastic method should be tried.

Cases of extra-laryngeal tumours in which a large carcinoma was present in the pyriform sinus could very well be treated by radiotherapy. He doubted whether it was

possible to define clearly the indications for treatment in each case. He thought it would be useful to collect the various results. The radiologist endeavoured, and with a certain success, to get gramophone discs of the voice before and after his treatment, and, of course, the X-ray treatment gave better results so far as the voice was concerned than operation. But there was always the question of the late results, and he doubted whether any complete judgment could at present be made. Only the previous week a patient died who had been treated for an endolaryngeal carcinoma by radiotherapy, and he was quite convinced that it would have been possible to have cured that patient by surgery. The death took place six years after the original treatment. The treatment was followed by a period during which the patient was relatively well, but he got a recurrence and died very miserably.

Professor M. Hajek (late of Vienna) said that he could not give the figures of his own cases because they were very complicated. The total number was 385 cases of carcinoma of the larynx, but he could not now say what were the results of these cases since he left his clinic. He advocated surgical operations so long as these were possible. Mutilation had been referred to, but this had different meanings for different patients. What would be considered dire mutilation by one would not be so regarded by another. With many of his patients who had undergone laryngectomy it would not have been supposed at a glance that they were suffering from an extirpation of the larynx. He was convinced that in carcinoma only operation could help. He had cases living after this operation for fifteen years and one case living for over twenty years. He had seen cases treated with radium demonstrated by his colleagues, but it had been his experience that a very few years later the carcinoma had recurred. The appearance immediately after the radium or X-ray application did not prove anything. It was true that the tumour had diminished, but one had only to wait to see a recurrence.

N. S. Finzi said that the statistics of surgery and of radiology were not really comparable, as the types of case treated were usually different. A most important publication had just been issued from the Christie Hospital and Holt Radium Institute, Manchester, giving five-year results in cases treated in 1932-3. These results should be studied with the greatest care by all members of the Section.

Mr. Stebbing had mentioned geographical difficulties; he would like to mention the biological ones. One obtained completely different results with an intrinsic carcinoma of the larynx from those which were obtained with an extrinsic. The intrinsic was far more favourable, even though it had become so extensive as to eat through the cartilage. He had had great difficulties with carcinomas of the pyriform fossa. Although he had some cases which had remained alive for five years, these were very few, and one was inclined to the view that the Trotter operation should be done in these cases, where practicable, even if one subsequently used radiotherapy as a means of eliminating any carcinomatous remnants. There were bound to be many disappointments and bad results as well as good.

F. Holt Diggle said that within the last seven years he had had the privilege of being associated with one of the best equipped radium institutions in this country, namely the Manchester Holt Radium Institute. He considered at the outset that if they were going to give radium a chance it was essential to have perfect teamwork. Each case should be seen by a surgeon, by an expert radiotherapist, and by a pathologist, to decide whether radium or surgery would offer the best chance of recovery. For many years radiation therapy was only regarded as palliative treatment and applied to the inoperable case, so the results were extraordinarily poor. With good teamwork the results were rapidly improving.

The two forms of therapy could be compared statistically by taking them case for case—it was purely a question of spread. It was unfair to either form of therapy to compare large massed groups.

For comparative purposes it was necessary to consider cases regionally taking them group by group.

In malignant disease of the nasal sinuses he felt that the results were probably in favour of surgery. He had a few cases on record who were alive and well to-day after Moure's operation. Radium could not at present produce as good results. It led to troublesome necrosis of the superior maxilla and other complications.

In the nasopharynx there was no doubt that radiation gave results far superior to any

surgical procedure. He had now four patients with malignant disease of the nasopharynx, with all the typical signs, who were alive and well to-day after five years.

When, in 1935, he collected statistics for a comparative review of Radiation versus Surgery in the treatment of laryngeal cancer he discovered that of 126 cases of extrinsic and extensive intrinsic cases treated by radiation, only three survived twelve months and all three were epilaryngeal growths—that is, a growth of the epiglottis and the aryepiglottic folds. That experience taught one the lesson that lesions limited to the epiglottis or spreading a little on to the aryepiglottic folds were particularly amenable to radiation, and such had been borne out by subsequent figures published by the Christie Hospital. It was purely a question of accessibility.

He had said that of 126 severe intrinsic and extrinsic cases all were dead within a year with the exception of three epilaryngeal cases. The position had altered greatly with the improvement in technique, in apparatus, and in the use of increased voltages. He had to-day several cases of very advanced disease of the interior of the larynx alive after three years. This work had not continued sufficiently long to give five-year figures, but he was convinced that the treatment for extensive intrinsic disease was deep X-ray therapy.

When it came to extrinsic growths, as in the post-cricoid region, it was another problem. Here it was purely a question of access. It was an open question which was the better. In expert hands such as those of Mr. Colledge operative treatment probably offered the best chance. With regard to the pyriform fossa and the aryepiglottic growths, these gave surprisingly good results with deep X-ray therapy, but he considered they could be improved if the first stage of the Trotter operation were adopted and access to the growth produced by removing the posterior three-fourths of the alar cartilage on that side. Ten years ago he had a case of pyriform sinus growth, in which he excised the posterior three-fourths of the alar cartilage and put in radium implants. About a year afterwards that patient came up with severe dysphagia and a sloughy growth in the region treated, with fixation of the cord. He felt that this was undoubtedly a recurrence. Further examination, however, proved it not to be a recurrence, but sloughs over scar tissue, which could be easily scraped away. In pyriform sinus cases access to the region should, he considered, first be gained by resecting the posterior half or three-fourths of the thyroid cartilage.

Somerville Hastings said that with regard to intrinsic carcinoma he started with a very strong prejudice in favour of surgery, but to-day in a case of intrinsic carcinoma of the larynx, either early or late, he would choose radiological treatment. He had had a few cases of intrinsic growths, again both early and late, in which radium or other radiation had failed to give any result. He recalled two cases at the moment. One case he submitted to thyrotomy and the other to complete laryngectomy, and in both cases he had no reason to regret the previous application of radiation.

As regards treatment, the implantation of radium or radon needles was very unfavourable. In one case in which he had carried out thyrotomy, only after seven years was there a new growth at the same spot. Then, because the patient was averse to further excision, radium needles were implanted, but the results were not favourable. On the other hand, with the radium beam and X-rays much more satisfactory results had been obtained.

A good deal had been said in the discussion about laryngectomy, and the suggestion had been made that it was an operation which should rarely be performed. He disagreed with this entirely. He thought that for carcinoma which did not respond to radium it was abundantly justifiable, but all depended on whether the patient was required to use his voice to any large extent. If the patient was one who had to use his voice largely he might get some relief from an artificial larynx, though he would not talk as happily as he did before. But he could show a good many cases in which he had excised the larynx during the last twenty years, and the patients were fairly happy to-day, and if they were asked he did not believe that one of them would reply that he was sorry he had had his larynx excised.

V. E. Negus said that he himself sent many patients for radiotherapy, but he was careful always to tell the patient beforehand that he was going to have a very uncomfortable time. He would not advise anybody to have treatment save by the protracted fractional method, which might occupy four or six weeks, and that was a great strain on

the patient. The operation of laryngofissure to his mind upset the patient much less than treatment of the same growth by radiotherapy. A list should be prepared of those cases which were made worse, by surgery or by radiotherapy. He had at times been extremely sorry that he had advised cases to be treated by radiotherapy. The growth had come back after one or two years; unless the patient had a good prospect of being cured by radiotherapy, he would not advise him to undergo that treatment.

The next point was that in some cases, as in the floor of the mouth and the tonsil, intermediate lymphatics might be involved and might not be capable of being dealt with by surgery, and here he thought that the rationale of radiotherapy was more reasonable.

In the nasopharynx he thought radiotherapy was the best treatment, and in this he included tele-radium and deep X-ray therapy. In the floor of the mouth the same thing held good. There should be preliminary treatment with radiotherapy, and the residuum of the primary growth could be dealt with easily by excision or diathermy if necessary. In the tonsil there were good results with radiotherapy, and local application of diathermy or radium needles might be useful for any residua. In the pharynx, and in the pyriform fossa particularly, the results he had had previously from pharyngectomy were very poor. He had seen many cases treated by radiotherapy also with bad results. If a patient had an extensive growth involving the pyriform fossa he would not advise him to have any treatment with a view to curing the disease.

In the larynx he thought that in the case of a growth of low-grade malignancy not involving the whole cord, laryngofissure was preferable, though these were not operations to be done by everyone. The upset to the patient was slight and the results were good. When the growth extended right along the cord, then he would advise radiotherapy. To take out the larynx was an unpleasant operation, often with good surgical results but bad psychological effects. There were cases of suicide which followed that operation. When the growth was widely spread and of a low grade of malignancy, however, total laryngectomy might still be performed because the area was a difficult one to treat by radiotherapy, owing to its enclosure by the partly cartilaginous and partly ossified framework. One had to deal with each individual region; in some cases the circumstances pointed to the advantage of surgical measures, while in others such measures seemed doomed to failure. But he wished to add that he had never seen in these regions such a thing as palliative radiotherapy.

G. F. Stebbing, in replying on the discussion, said that it was clear to him that Mr. Colledge deceived himself with his statistics. In his opening paper he, Mr. Stebbing, had tried to point out that in his large number of cases—nearly 400—it was necessary to divide and subdivide until one got some 50 or more different classes, so that the numbers in each were so small as to be statistically unreliable. These groups might be made larger by adding them together, but that would only disguise the fact that the error was being preserved. But Mr. Colledge had drawn conclusions from figures which were not comparable. He had first referred to his own highly selected group of operable cases, and he had compared it with a large group of cases entirely unselected, handled by a large number of different radiotherapists spread all over the country. The M.R.C. table had extended from 1925 to 1937, and during the early part of that period many clinics were only making tentative efforts in radiotherapy, and the cases embodied in the table must have included some of the very first to be treated at those clinics. Mr. Colledge had afforded a very good example of the entire unreliability of trying to draw conclusions from statistics, and it was astonishing that anybody should be deceived by that comparison.

The second point was that Mr. Negus, among others, had said that he did not believe it was wise to recommend people to have palliative radiotherapy in these hypopharyngeal growths. Quite frankly, he could not understand that position. Nobody knew better than he the disastrous results which had been produced in the past by ill-advised radiotherapy, and it was true to say that he had seen equally bad results by ill-advised surgery. But if one was going to use palliative radiotherapy there was no reason whatever why a patient should ever suffer anything as a result of that. The work done in twenty different clinics throughout the country and in many clinics abroad, where patients in considerable misery had been relieved of their symptoms for months and years, whose recurrences had never again been local, and who had died only of distant metastases—all these facts suggested the contrary to what Mr. Negus had stated. It was not generally known that

a recurrence of carcinoma in the scar of a lesion healed by radiotherapy often had the appearance of a necrotic ulcer, and caused a great deal of pain.

Radiotherapy was always a long and laborious business, but in the region of the body under discussion, even successful surgery left a disability. It might be said to the patient, "You have very little trouble, you are only hoarse", but the patient thought of it as being always hoarse, and in those very cases in which one could take away by surgery a small lesion and leave the patient with hoarseness, treatment by radiotherapy could with a great degree of certainty cure the disease and leave no hoarseness at all.

CORRIGENDUM.

Proc. Roy. Soc. Med., 33, 584 (Section of Dermatology, p. 8).

Discussion.—Dr. F. PARKES WEBER.

Line 7. *After* " . . . a case for him." *insert* "At that meeting one of the cases which attracted most notice and caused a great deal of discussion was apparently a case very like this", . . .

Section of Therapeutics and Pharmacology

President—Sir WILLIAM WILLCOX, K.C.I.E., C.B., C.M.G., M.D., F.R.C.P.Lond.

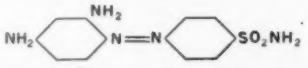
[*June* 11, 1940]

DISCUSSION ON CLINICAL EXPERIENCES WITH SULPHATHIAZOLE IN THERAPY OF STAPHYLOCOCCAL INFECTIONS

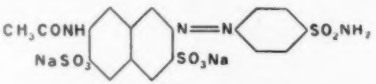
Dr. A. J. Ewins: *Some introductory remarks on sulphonamides.*—This meeting is concerned with the treatment of staphylococcal infections with especial reference to the use of a new chemotherapeutic agent of that class of compounds now generally known as "the sulphonamides". This new product, to which the name sulphathiazole has been given by its sponsors in the U.S.A., has recently been the subject of a number of publications in that country, both experimental and clinical, in which it has been claimed that the drug has certain advantages over the hitherto known sulphonamide derivatives, particularly as an effective agent against the staphylococcus and also as an antipneumococcal agent which is at least as effective as sulphapyridine and is moreover better tolerated and of lower toxicity than the latter.

It has been suggested to me, therefore, that it would be of interest to you if I were to indicate the development, from the chemical point of view, of this and some of the better-known sulphonamide compounds which have come into clinical use since the original epoch-making discovery by Domagk of the *in vivo* anti-bacterial activity of "sulphonamido-chrysoidine" the original Prontosil, later known as Prontosil Red.

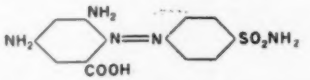
This compound was first synthesized by Mietzsch and Klarer [1]. It has the formula



and is a red "azo dyestuff". In 1935 Domagk [2] published a full account of its anti-bacterial action and showed that it could effectively afford protection to mice infected with a virulent strain of *Streptococcus hæmolyticus*. It was also shown to exert some curative action against staphylococcal infections in mice. Two other closely related products which have found clinical application are Prontosil Soluble



shown by Domagk to be an effective anti-streptococcal agent and a French product, Rubiazol,



which was studied by Levaditi and Vaisman [3] and found to be similarly active.

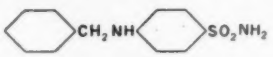
Tréfouël, Tréfouël, Nitti, and Bovet [4] from the study of a large number of azobenzene compounds showed that only those derivatives which contained a sulphonamide group attached to a benzene nucleus were active. They then deduced that these compounds were broken down in the organism with formation of p-aminobenzenesulphonamide and showed that this product itself exhibited an activity comparable with the most active of the original

azo-dyes. This observation was quickly confirmed by Goissedet, Despois, Gailliot and Mayer [5] in France and, in this country, by Buttle, Gray and Stephenson [6] as well as by Fuller [7] who also showed conclusively that p-aminobenzenesulphonamide is formed in the tissues when prontosil red is administered orally to animals or to the human subject.

p-Aminobenzenesulphonamide, which is now generally known as sulphanilamide, is not a new compound but was first prepared as long ago as 1908 by Gelmo [8]. It is now probably the most widely used of all the compounds of this class. The discovery of its activity, not only as an anti-streptococcal agent, but also as a curative agent against meningococcal, gonococcal and to some extent pneumococcal and staphylococcal infections stimulated research in this field to an enormous degree and it was not long before derivatives were prepared for which claims for lessened toxicity and other advantages were made.

Among these, two products known in this country as proseptasine and soluseptasine respectively have found clinical application.

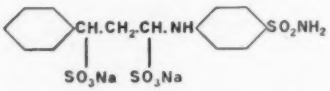
Proseptasine is p-benzylaminobenzenesulphonamide,



and was first prepared by Goissedet and his collaborators [5].

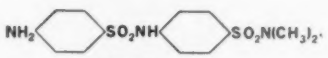
The efficacy of the drug as an anti-streptococcal agent was confirmed experimentally by Whitby [9]. It is one of the least toxic of the sulphonamide compounds and has been successfully used in the treatment of streptococcal infections, such as streptococcal meningitis, erysipelas, tonsillitis, &c.

Soluseptasine is the disodium salt of p-(γ-phenylpropylamino) benzene sulphonamide α-β-disulphonic acid



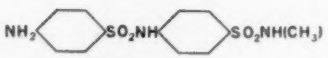
It has the advantage of being readily soluble in water, giving a neutral solution and is readily hydrolysed, giving rise to sulphanilamide. It is in fact an effective soluble form of the latter drug.

A further contribution to the study of these compounds was made by Domagk [10], by the investigation of a series of products which were described as Diseptal A, Diseptal B, and Diseptal C, of which Diseptal A is better known as Uleron. They have the formulæ

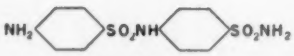


DISEPTAL A.

(ULERON)



DISEPTAL B



DISEPTAL C

and may be regarded as derived from combination of two molecules of sulphanilamide and substitution of the hydrogen of the terminal sulphonamide groups by one or two

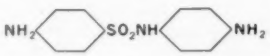
methyl groups. It was claimed that these compounds were as effective as sulphanilamide as anti-streptococcal agents, but that there was a striking increase in efficiency against staphylococcal infections in all three compounds. Uleron has been used to some extent for the treatment of gonorrhœa but is liable to produce a form of peripheral neuritis.

A product which has also been introduced for the treatment of gonorrhœa is known as Albucid. It is a p-aminobenzenesulphonacetamide

an acetyl derivative of sulphanilamide in which the acetyl group is substituted in the sulphonamide group in contrast to the acetylamino derivative which is formed in the organism when sulphanilamide is administered to animals or man.

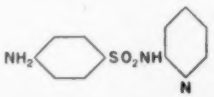
The researches carried out in our own laboratories started from an observation by Buttle [6] and his collaborators, who showed that p-aminobenzenesulphonanilide was an active anti-streptococcal derivative of sulphanilamide. This product has the formula

in which a phenyl group is substituted for one of the hydrogen atoms of the sulphonamide group. Previous investigations carried on in Fourneau's laboratory in Paris [11] had shown that further substitution in the benzene nucleus of p-aminobenzenesulphonamide resulted invariably in diminished anti-bacterial activity of the resulting compound and also that the para position for the amino group in relation to the sulphonamide group was essential for maximum activity. It by no means followed, however, that substitution in the terminal benzene nucleus of Buttle's compound would not lead to enhanced activity. A number of such substituted compounds were therefore prepared and it was found that the introduction of an amino group into this nucleus did in fact result in increased anti-streptococcal activity, the product p-p′ diaminobenzenesulphonanilide



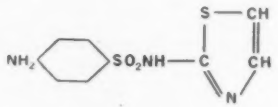
being found by Whitby [9] to be as effective as sulphanilamide as an anti-streptococcal agent. The isomeric compound p-m′ diaminobenzenesulphonanilide was found to be equally active. The toxicity of these products, however, precluded the possibility of clinical trial.

In these compounds one of the hydrogen atoms of the sulphonamide group is substituted by the basic aniline group and this suggested that substitution by the other basic groups might be generally advantageous. Our investigations were therefore directed to the preparation of derivatives in which the aniline substituent was replaced by such basic groups as pyridine, quinoline, isoquinoline, &c. The first compound of this type to be prepared was 2-(p-aminobenzenesulphonamido) pyridine,



the compound which is now generally known as " sulphapyridine " or M & B 693. This was found by Whitby [12] to be equal to sulphanilamide as an anti-streptococcal agent but far superior to it as an anti-pneumococcal agent, affording a high degree of protection to mice heavily infected with pneumococci of various types [1]. Of the clinical success of this product not only as an anti-pneumococcal drug but in the treatment of streptococcal, meningococcal, gonococcal, and other infections, the literature of the last two years bears adequate witness. Successes in the treatment of staphylococcal septicæmia have also been recorded.

A very considerable number of variously substituted pyridine and quinoline derivatives of this type have since been examined. Many of these showed varying degrees of antibacterial action. None has proved to be experimentally superior or even equal to sulphapyridine as anti-pneumococcal compounds, although some few have been found to be antistreptococcal to a marked degree. The results obtained with sulphapyridine led us to turn our attention to other heterocyclic basic derivatives of sulphanilamide and early in 1938 one of my colleagues, Mr. G. Newbery, prepared the corresponding thiazole compound 2-(p-aminobenzenesulphonamido) thiazole or "sulphathiazole".



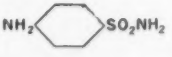
It was investigated by Whitby for anti-streptococcal and anti-pneumococcal activity in infected mice and was obviously a product of considerable interest. It was as effective as sulphanilamide and sulphapyridine against *Streptococcus hæmolyticus* in the experimental animal, but a close comparison of its pneumococcal action in infected mice led us to the conclusion that while superior to sulphanilamide in this respect, it was definitely less active than sulphapyridine. No really satisfactory method for the comparative evaluation of these drugs against staphylococcal infections appeared to be available just then and experimental work in that direction was not, at the time, undertaken. The clinical assessment of the value of these drugs in human staphylococcal infections is likewise not likely to be easy, and it would appear that only experience will show whether the hopes aroused by the introduction of this compound will be justified.

Research on these products which began in Germany, and was continued in France and in this country, has now inevitably become mainly centred in the U.S.A. During the past few years a number of publications dealing mainly with the chemical aspect of the subject have appeared. Although claims have been made for many of the compounds described as being of considerable activity against bacterial, and even in some cases, virus infections, the sulphathiazoles alone appear to have attracted widespread interest or to have achieved any clinical success.

A recent paper by Fildes [13] suggests that the sulphonamides and other bacterial compounds most probably act by specific interference with metabolites essential for the growth of bacteria. Woods [14] has shown for example, that p-aminobenzoic acid, a constituent of extract of yeast, which is also for other reasons regarded as an essential metabolite for bacteria, counteracts the action of sulphanilamide *in vitro* while Selbie [15] has shown that it can also neutralize the curative action of sulphanilamide in mice infected with a *Streptococcus hæmolyticus*.

Arguing from the structural similarity between

p-aminobenzoic acid

and sulphanilamide 

and drawing attention to the fact that sulphapyridine, like nicotinic acid, contains a pyridine group, and sulphathiazole, like vitamin B_1 a thiazole group, Fildes suggests that chemotherapeutic research might well be directed to making "such modifications of known essential metabolites" as will have the characteristics which he suggests as necessary for successful interference with these substances. It is perhaps of interest to note that nicotinyl p-aminobenzene sulphonamide and 2-(p-aminobenzene sulphonamido) pyridine (the pyrimidine ring being also a constituent of vitamin B_1) have recently been prepared in the U.S.A. and are stated to be active anti-bacterial compounds of low toxicity.

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Mr. E. C. B. Butler: Staphylococcal septicæmia is a much more common and more fatal condition than many people realize. Every death from osteomyelitis, nearly every fatality from cavernous sinus thrombosis and many from boils, carbuncles and infected fingers can be attributed to the *Staphylococcus aureus*. These fatal cases are often sudden in onset and death may take place in two or three days from an overwhelming staphylococcal bacteriæmia. Any treatment to be effective must therefore be started at the beginning of the disease; a patient whose blood culture runs into hundreds of colonies of staphylococci per c.c. is generally past all therapeutic aids.

During the last eight years 51 patients died at the London Hospital of bacteriæmia which arose either from osteomyelitis, boils, carbuncles or infected fingers. 40 of these were due to the *Staphylococcus aureus* and only 11 to the hæmolytic streptococcus. Staphylococcal bacteriæmia is very much more common and equally as fatal as hæmolytic streptococcal blood-stream infection.

Any treatment which is claimed to cure staphylococcal infections must either be able to cure patients who already have a positive blood culture or else accelerate recovery in those lesions which experience has shown may give rise to bacteriæmia, e.g. carbuncles of the face.

In these severe cases we must first try to raise the resistance of the serum to the toxins produced by the staphylococcus. Dr. Valentine has shown almost conclusively that the leucocidin is the important toxin and also that the majority of patients have a low anti-leucocidin content in their blood for the first few days of the disease in severe types of infection. We therefore now give to every patient with a severe staphylococcal infection 25 c.c. (about 20,000 units) of staphylococcal antitoxin with a high anti-leucocidin content Secondly can we give any drug which may help in the destruction of the staphylococci once the patient's resistance has been raised either naturally or by antitoxin. I have used sulphanilamide, sulphapyridine and uleron but have been unable to satisfy myself that any of these drugs affected the course of the severe cases. Sulphathiazole next came into prominence owing to the work done on it in the United States and I eagerly welcomed the opportunity to try it. Thirdly the problem of eliminating the focus from which comes the blood infection in those patients with a persistent or increasing bacteriæmia must be solved at the earliest moment. This may be accomplished either by adequate drainage, by excision or by amputation. I have had a few cases where dramatic recovery and a sterile blood culture followed removal of a comparatively insignificant focus of infection. Once the source of the bacteriæmia is eliminated the resistance of the patient may well be able to deal satisfactorily with the remaining systemic infection. Up to the present I have only been able to treat five cases with sulphathiazole. All were severe infections and afforded a good clinical test of the drug. Milder staphylococcal infections generally recover spontaneously or with surgical drainage and afford no real test for new means of treatment.

Case 1.—Woman, aged 62.

2.2.40: Six days ago she pricked her finger which became painful.

On examination.—Signs of a sheath infection, finger was freely incised. Pus not sent for examination.

9.2.40: Continued pyrexia; sulphanilamide given; no response. Clinical condition deteriorated and patient became at times irrational. Repeated courses of sulphanilamide given with no benefit.

18.3.40: A blood culture was positive to *Staphylococcus aureus*. White count 12,000.

22.3.40: I first saw this patient. Irregular temperature; no apparent active infection of finger.

23.3.40: Course of sulphathiazole started. Four tablets stat. and then two tablets four-hourly for four days. (1 tablet (M & B) = ½ grm.)

27.3.40: Blood culture positive. Eight colonies per c.c.

31.3.40: Amputation of finger followed by another course of sulphathiazole.

3.4.40: Blood culture negative and temperature normal.

17.4.40: Patient died rather suddenly.

Post-mortem.—No active focus of infection or signs of septicæmia.

Comment.—The first course of sulphathiazole apparently made no appreciable difference to the infection as the blood culture was still positive after its administration. After removal of the presumed source of the bacteriæmia combined with a second course of the drug the blood culture became negative and remained so until her death, which was due to cardiac failure.

Case 2.—Man, aged 55.

Seven days' pain and swelling of face following biting of inside of cheek.

15.4.40: Ill; gross infection of left face and upper lip. Blood culture sterile on two occasions.

16.4.40: Two large abscesses drained on face. Culture: *Staphylococcus albus* and *Streptococcus viridans*.

20.4.40: Full course of sulphathiazole given. During this course he had two rigors and clinical condition did not improve.

24.4.40: Sulphathiazole stopped and not repeated. Orbital cellulitis gradually localized and was drained. Face and orbit rapidly improved after last drainage.

12.5.40: Developed acute dyspnœa and signs of pneumothorax. Chest needled and pressure relieved. Pressures −6 and +6. X-ray next day confirmed air in chest.

13.5.40: Chest again needled. Pressures −8 and +4.

14.5.40: Death.

Post-mortem.—Œdema of brain but no active infection of brain, meninges or cavernous sinus. Pyopneumothorax from two small pyæmic abscesses in lower lobe of right lung. One of these had a macroscopic perforation into pleural cavity.

Comment.—No definite improvement followed sulphathiazole administration, possibly owing to the mixed type of infection.

Case 3.—Woman, aged 70.

Four days' swelling of face and eyes after injury.

Ill; severe pustular infection of face around both eyes and forehead. Several purulent blisters also on hands. Blood culture was negative. Pus from blisters contained *Staphylococcus aureus*.

Sulphathiazole 30 grm. in all was given for one week after admission. There was no definite change for the better. The patient gradually became weaker and died of bronchopneumonia which was confirmed at post-mortem.

Comment.—Sulphathiazole did not seem to improve the local skin condition.

Case 4.—Woman, aged 32.

26.4.40: Three days ago burst a varicose vein in her leg which soon became very painful. Severe cellulitis of leg with a small ulcer at the site of the burst vein. This was mistakenly incised and no pus was found.

27.4.40: I first saw her; there was a severe unlocalized cellulitis of leg with slight discharge from the operation wound. Culture from this showed pure *Staphylococcus aureus*. Blood culture was negative. 20,000 units of antitoxin were given intramuscularly. Full course of sulphathiazole given till 30 grm. had been administered.

Her condition rapidly improved and she required no further surgical intervention.

Comment.—The rapid improvement of her general and local condition was quicker than could have been expected in an untreated case.

Case 5.—Boy, aged 12.

17.5.40: Four days ago had small pimple in nostril.

Child very ill with pustules on upper face and gross œdema of upper face and eyelids.

No signs of meningitis. Culture from pustules showed *Staphylococcus aureus*. Blood culture was positive to *Staphylococcus aureus*.

18.5.40: 20,000 units of staphylococcus antitoxin given intramuscularly. 1 grm. of sulphathiazole given intravenously and 1½ grm. by mouth every four hours until 30 grm. had been given. At the end of this course his condition had not improved, he had marked proptosis and signs of meningitis.

23.5.40: Blood culture was 140 colonies per c.c. Lumbar puncture showed cloudy fluid under tension with excess of cells, and culture grew *Staphylococcus aureus*. Daily lumbar puncture was done for five days. At the end of that time the fluid was clear and sterile but the patient had developed a hemiplegia.

29.5.40: Pneumothorax. 850 c.c. of air withdrawn from right chest.

31.5.40: 680 c.c. of air from right chest and 160 from left chest.

3.6.40: 940 c.c. of air from right chest and 300 from left side.

5.6.40: 800 c.c. of air from right chest.

Blood cultures were as follows—24.5.40: 130 colonies. 27.5.40: 50 colonies. 30.5.40: 25 colonies. 1.6.40: 2 colonies. 5.6.40: Sterile.

Further course.—Signs of meningitis reappeared and despite repeated aspirations of both sides of his chest bilateral pneumothorax persisted.

22.6.40: The patient died.

Post-mortem.—Bilateral pyo-pneumothorax; multiple lung abscesses; extra- and intradural abscesses and focal leptomeningitis. Purulent thrombosis of superior ophthalmic veins. Pyæmia.

Conclusions

The treatment of staphylococcal infections is more difficult than that of the hæmolytic streptococcus. In streptococcal infections we have a drug which can inhibit the full development of the organism, particularly when the immunity of the patient's serum is raised. In staphylococcal infections, however, although by antitoxin we can raise the patient's resistance against the invading organism, I do not think we have as yet found a drug capable of affecting the staphylococcus as sulphanilamide affects the streptococcus. Sulphathiazole seems to have little or no beneficial effect on staphylococcal infections where there is a positive blood culture. It may be of benefit in patients where the septic focus has been removed or who are suffering from a localized lesion such as a carbuncle or cellulitis. Further examples of such cases should receive treatment in the hope that the incidence of bacteriæmia in these patients may be reduced. Since in my experience all deaths from staphylococcal infection are due to bacteriæmia and its complicating abscesses it does not appear at present that sulphathiazole will appreciably lower the high mortality of these cases. In all cases early bacteriological diagnosis is essential, supplemented by quantitative blood cultures when possible in cases with bacteriæmia.

Sulphathiazole if tried should be given in adequate doses: a minimum dose of 2 grm. at the start and 2 grm. four-hourly until an average of 30 grm. has been given. In severe cases 2 grm. two-hourly would not be an overdose provided that a differential white cell count be made at the end of the second day. Lastly these drugs should not supplant conservative surgery or the giving of adequate antitoxin when that is available.

Dr. H. Moreland McCrea: My two cases, both septicæmia following carbuncles, treated with sulphathiazole, differ in two important points, in that the first had his first dose of sulphathiazole six weeks after the appearance of the carbuncle and in the second it was given on the tenth day.

Case 1. W. H. S., male, aged 40, first seen January 30, 1940, suffering from a carbuncle on the back of the neck the size of a half-crown. This exuded pus from multiple follicles, and there was much infiltration in surrounding tissues. The carbuncle gave a pure growth of *Staphylococcus aureus*. The patient was a heavy cigarette smoker and his alcoholic intake was at times above the normal. He gave no history of trouble with his bowels or kidneys and there was no past history of any serious illness. He owns and manages a large engineering works.

On examination.—Nothing abnormal was found. There was no septic focus in upper air passages. His blood-sugar at 4.30 p.m. was 163 mgm. per 100 c.c. but the next day the figure for his starving blood-sugar was 102·6. He was treated on the usual conservative lines of fomentations, &c., and was not submitted to any surgical interference. At the end

of a week when he left the nursing home his general condition was good. There was a small area of healthy granulations at the site where the carbuncle had been. The following day he complained of very severe pain in the left ilium over an area about the size of the palm of the hand, 2 to 3 in. below the crest of the ilium and 2 in. from the sacro-iliac joint. Palpation over this area revealed nothing definite beyond some thickening of the tissues. Tenderness was exquisite over one spot about the size of a shilling in the centre of this area.

He was then readmitted to the nursing home. The pain became more intense and at the end of the first forty-eight hours was radiating down the front of the thigh. Reflexes at this time were quite normal. Twenty-four hours later, the nineteenth day of the illness, the temperature which had been round the normal mark suddenly rose to 105° but no rigor occurred and blood taken at the height of the rise remained sterile on culture. Leucocyte count rose to 16,000 with 91% polymorphonuclears. The temperature was not accompanied by any localizing symptoms and in three days was again normal. On the twenty-sixth day of the illness the temperature rose suddenly to 104° with a severe rigor. Blood culture again proved sterile but many *Staphylococcus aureus*, the same type of organism as that grown in pure culture from the carbuncle, were found in the urine. Here this organism was found continuously till the temperature finally reached normal but its presence was never associated with pus in any considerable quantity. On the twenty-eighth day he expectorated a small quantity of sputum which gave a heavy growth of *Staphylococcus aureus*. The pain in the ilium had continued in great severity up to this time and had extended down the front of the thigh as far as the knee-joint. Both elbow-joints now became involved causing exquisite pain on movement. No X-ray evidence of any lesion was found in the ilium or in the joint but an abscess was discovered on the right side in the ascending ramus of the pubic bone. This was opened and drained. No organisms were grown from the fluid contents of this small cavity, but a piece of degenerate bone gave a pure culture of the same type of organism already found in the carbuncle. Six days later, the thirty-fifth day of the disease, both elbow-joints became distended with fluid. These were aspirated and again the same type of organism was found on culture. Expectoration now became more excessive: again the organisms were found. This was derived from the right base which showed some crepitations; at no time was there any evidence of an infarction. The first dose of sulphathiazole was given on the fortieth day of the disease, when the patient's general condition was deteriorating. 6 grm. were given in the first twelve hours and then the dose was reduced to 1 grm. four-hourly.

The improvement in the patient's condition showed itself in the first twenty-four hours. Seventy-two hours after the first dose was given the splints, which had been necessary on both elbow-joints, were temporarily removed and active movements of both joints were performed without pain. This improvement held till the sixth day when a circumscribed swelling appeared in the triceps of the left arm. After 25 grm. had been taken the sulphathiazole was stopped owing to extreme nausea and to the fact that the urine was becoming scanty and contained some microscopic blood and granular casts. During the next few days the swelling in the arm became much larger and very tender till it was about the size of a hen's egg; this was associated with a temperature, though never above 101°. Four days after the last dose of sulphathiazole it was started again. 2 grm. were given and repeated four-hourly. In the next twenty-four hours multiple painful raised red papules about the size of a shilling appeared on the front of the right tibia and a small swelling was palpable at the insertion of the deltoid muscle. The second course was continued for six days but owing to the return of nausea it was not possible to give it four-hourly with any regularity. At the end of this period the temperature was normal and all symptoms were improving. During this second course he took in all 23 grm. Convalescence now followed. There were no further rises of temperature: the painful papules disappeared and the swellings in the arm gradually subsided. Marked wasting of the muscles all over the body had occurred and on getting him out of bed it was found that he had loss of power in the extensors of the right knee-joint and he still had tenderness in the right buttock within the previously painful area. It was concluded that this pain had been due to a toxic neuritis of the 2nd, 3rd and 4th lumbar roots. With faradic treatment combined with massage and exercises the muscles involved are now practically normal. The anæmia which developed in the latter part of his illness has gradually improved and his blood picture is now normal. His joints show normal painless range of movements and all his swellings have disappeared leaving no trace.

Considering the train of symptoms this can be accepted as a true case of septicæmia although the blood examination proved sterile. It may be argued that there is not sufficient evidence that the sulphathiazole arrested the infection, for it can be said that

the patient's immunity to the poison was being gradually built up before its administration but the striking points in favour of the curative powers of this compound are : (1) After its administration the purulent fluid did not again collect in the elbow-joints and these to-day show a normal range of movements. (2) The large swelling in the triceps muscle did not break down and form an abscess as might have been expected. (3) The swelling in the deltoid never assumed serious proportions and quickly disappeared. (4) The organisms disappeared from the urine after the second course of sulphathiazole.

Case 2. Miss G. G., aged 33, came under my care ten days after a carbuncle appeared on the back of her neck. It was large and deep with much infiltration around and was discharging freely.

Past history.—Nothing noteworthy.

On examination.—General condition excellent. Culture of pus from the carbuncle gave a pure growth of *Staphylococcus aureus*. Blood-count showed 5,050,000 R.B.C. and 24,687 W.B.C., 80% of which were polymorphonuclears. Blood-sugar was 132 mgm. per 100 c.c. Treatment on conservative lines was adopted. The day after admission to the nursing home the temperature suddenly rose to 105°. Blood culture at the height of the temperature gave a pure culture of *Staphylococcus aureus*. Treatment with sulphathiazole was commenced, the initial three doses being 2 grm. four-hourly : unfortunately the patient began to vomit as a result of the drug and the intervals between doses became irregular and the dose itself was reduced to 1 grm. Apart from the carbuncle there was no definite lesion to be detected yet the temperature remained at a high level. This could have been accounted for by the acute spreading inflammatory process at the base of the carbuncle.

Sulphathiazole was stopped after six days : in all 28 grm. were given. On the second day after the first dose of the drug the temperature showed signs of dropping but on the fourth day it suddenly rose again to 103° associated with acute pain in the epigastrium radiating round the left lower costal region. There was also marked distension of the abdomen and loss of breath sounds in the left lower chest. Blood culture was negative. Leucocytes rose to 20,312 after these had been showing a steady fall, polymorphonuclears being still 86%. Administration of tablets was again commenced but only continued for twenty-four hours. The breath sounds gradually began to come through at the base of the left lung three days later. About the same time the patient produced a large plug of sputum typical of that associated with an infarction. The old blood-clot in this sputum gave a pure growth of *Staphylococcus aureus*. The patient now made slow and steady progress till she left the home at the end of the seventh week of her illness. The lung gradually cleared but an X-ray before she left showed thickening round the bronchioles but no evidence of fluid or an abscess cavity. We found while giving the tablets granular casts and some blood in the urine but only on three occasions were the organisms found in any quantity.

A few days after she left the home she twisted the right knee-joint which rapidly filled with fluid. The doctor in charge aspirated it but he found only a clear serous fluid sterile on culture. In this case sulphathiazole was given before immunity against the infection was established; therefore the points in favour of the curative effect of the drug are : (1) The only complication was infarction of the lung. This was a septic infarction yet no abscess of the lung or empyema followed it. (2) No other complications occurred. (3) An injury to the left knee was followed by a sterile effusion.

The two difficulties in these cases were nausea as a result of the administration of the drug and a diminution in the secretion of urine, this latter containing granular casts and blood corpuscles. The amount of pus in the urine in both cases never assumed such proportions as to suggest a localized infection in the kidneys or their surroundings. A reduction of red cells in the blood was found in both, in the first case before the tablets were given and in the second after their administration. Since this grave infection has always been associated with a reduction of red cells, no conclusion can be drawn from these findings.

Dr. G. Melton : I have had the opportunity of treating six cases of osteomyelitis and five cases of carbuncle of the face with sulphathiazole.

Case 1.—I. S., female, aged 16. Acute osteomyelitis of the lower end of the radius and ulna. The infection followed open reduction undertaken for fracture. A culture of pus taken from the wound showed *Staphylococcus aureus, Streptococcus hæmolyticus*

and *B. welchii*. There was no clinical evidence of gas gangrene. The condition improved, but did not clear up after 21 grm. of sulphapyridine. Following a change of plaster with manipulation of the fracture, the temperature rose to 103·4°. Blood culture was negative. There was never any enlargement of the spleen or evidence of metastatic infection. Sulphathiazole was given, 1 grm. intravenously for four doses and then 1 grm. orally four-hourly. The total dosage employed was 26 grm. The temperature fell within twenty-four hours to 99·2, and never rose subsequently above this level. The wound infection gradually improved. X-rays showed osteomyelitis of the fragments of the radius and ulna with sequestra.

Toxic symptoms due to the drug.—The patient complained of headache and vomited after each injection. A rash resembling erythema nodosum appeared on the legs and arms, but subsided after twenty-four hours. The urinary output and urine were normal. The white cells fell from 15,000 per c.mm. to 4,500 after three days; five days after ceasing treatment, the white cell count rose again to 12,000 per c.mm.

Estimation of the drug in the blood.—Figures ranged from 0·8 mgm.% to 3·3 mgm.%.

Case 2.—S. P., male, aged 12. This patient had acute osteomyelitis of the lower end of the humerus with a sterile effusion in the elbow-joint. Blood culture was negative. The arm was placed in plaster. Sulphathiazole was given 1 grm. four-hourly up to a total of 48 grm. At the end of this period the temperature had not fallen. The plaster was removed and a large abscess was found, which on being incised was seen to extend down to the back of the humerus. *Staphylococcus aureus* was found in the pus. The temperature then fell and was normal within a few days. An X-ray of the elbow-joint showed no bony disease. There was no leucopenia during treatment and no toxic symptoms due to the drug. The drug in the blood showed levels ranging from 1·6 mgm.% one hour after 1 grm. of the drug to negligible amounts four hours after a similar dose. The urine remained normal.

Case 3.—B. C., male, aged 8. This patient had acute osteomyelitis of the upper end of the femur. The hip-joint was not involved. The blood culture was sterile. He was treated in a plaster spica. Following sulphathiazole therapy, 1 grm. intravenously, followed by 1 grm. four-hourly by mouth up to a total of 8 grm., the temperature rose from 99·6 to 102·2. The dose was increased to 2 grm. four-hourly and a further 8 grm. was given, but the temperature remained high. The drug was then given intravenously in doses of 1 grm. four-hourly, and as the child was very ill, the upper end of the femur was explored, but no osteomyelitis was found. Intravenous therapy was continued for six doses and the temperature fell at the end of this period to 98·8°, never subsequently rising above 99·4°. The child recovered completely. X-rays of the femur showed no definite evidence of osteomyelitis. No abnormal physical signs were found in any other system. The total dosage of the drug employed was 40 grm. The blood sulphathiazole estimations varied from 2·1 mgm.% after 1 grm. of the drug orally, to 4·4 mgm.% after 2 grm. orally and 5·5 mgm.% half an hour after 1 grm. intravenously. The white cell count fell from 21,500 per c.mm. to 6,500 per c.mm. forty-eight hours after commencing therapy, but rose to 17,000 per c.mm. four days after stopping the drug. There were no other toxic drug symptoms.

Case 4.—E. S., male, aged 19. This patient had a Brodie's abscess at the lower end of the femur, which was explored and drained. *Staphylococcus aureus* was found in the pus. Following the operation the temperature rose to 101·8. The blood culture was negative. Sulphathiazole therapy was carried out, 1 grm. intravenously followed by 2 grm. four-hourly orally for four days. The temperature gradually settled down and was normal two days after ceasing drug therapy. The local condition improved satisfactorily. There was no leucopenia and no toxic drug symptoms. Blood sulphathiazole reached a maximum of 5·4 mgm.%.

Case 5.—J. B., female, aged 11. Acute osteomyelitis of the ilium with suppurative arthritis of the hip. A blood culture grew *Staphylococcus aureus*. This girl had had rheumatism and there was evidence of rheumatic mitral disease. A plaster spica was applied and sulphathiazole therapy instituted. 1 grm. was given intravenously and followed by 1 grm. four-hourly for three days up to a total of 18 grm. After an initial fall of temperature from 104·2° to 98·4° after twelve hours, the temperature rose again. The dose of the drug was increased to 2 grm. four-hourly so that at the end of six days 44 grm. had been given. The blood culture remained positive, and there was no permanent fall in temperature. On removing the plaster a large abscess was discovered, which on incision was found to extend on to the outer side of the ilium. The pyrexia continued despite drainage. A second course of sulphathiazole, 22 grm.

in all, was given, but no improvement resulted. The hip-joint was then aspirated and pus discovered. The joint was then drained. As pyrexia continued a third course of the drug (12 grm.) was given, but this was stopped as there was no abatement in pyrexia. Signs of bronchopneumonia appeared. Following blood transfusion and staphylococcal antitoxin, there was a definite improvement with a fall in temperature. The pyrexia, however, recurred, and a course of sulphapyridine (25 grm.) was tried without any material alteration in the patient's general condition. The patient has since shown gradual improvement. The pulmonary symptoms have subsided and there have been no metastatic abscesses or evidence of bacterial endocarditis. A recent blood culture was negative. The urine has remained normal, apart from a faint trace of protein. The white cell count fell from 14,000 per c.mm. to 6,000 at one stage, but rose again to 10,000 after discontinuing treatment. The blood sulphathiazole level rose to 2·3 mgm.% on 1 grm. doses, and 5·8 mgm.% on 2 grm. doses of the drug. Pus from abscess contained only 1·3 mgm.% of sulphathiazole.

Case 6.—B.W., male, aged 50. A case of acute osteomyelitis of the femur with one metastatic abscess of the thigh and another in the knee-joint. The patient later developed a pathological fracture at the lower end of the femur. The blood culture was negative. A course of kiton green resulted in no improvement, and blood transfusions produced only temporary benefit. Sulphathiazole therapy was not introduced until late in the disease, i.e. not until after the drainage of the original focus and of the metastatic abscesses. *Staphylococcus aureus* was present in all of these. Sulphathiazole was given, 1 grm. intravenously for six doses and then 2 grm. four-hourly by mouth. The pyrexia declined and the general condition improved. There were no toxic drug symptoms. The assessment of the value of the drug in this case was complicated by the fact that the patient had recently developed a pathological fracture at the lower end of the femur, which was immobilized in a Thomas's splint just prior to commencing treatment with the drug. Blood sulphathiazole levels varied from 2 mgm.% to 8·3 mgm.%.

Case 7.—S. D., female, aged 71. A case of carbuncle of the chin and lower lip. This patient was very ill with pyrexia (102°-104°) before commencing treatment. The blood culture grew *Staphylococcus albus* repeatedly and the same organism was also grown from the carbuncle. Her blood urea was 96 mgm.%. She received 56 grm. of sulphathiazole over a period of one week, commencing with 1 grm. intravenously for three doses together with 2 grm. orally four-hourly. The temperature became normal within forty-eight hours and remained so. Repeated blood cultures remained positive until a few days after the drug was stopped. Two days after commencing treatment, the patient developed a pleuropneumonia, and later a serous effusion was aspirated, which grew the same organism. The carbuncle itself increased somewhat in size for several days, and then the condition cleared up and the patient is making a satisfactory recovery. No leucopenia developed. The blood urea became normal. The urine apart from a few casts showed no abnormalities. Blood sulphathiazole levels varied, but rose to a maximum of 13·2 mgm.% after 2 grm. of the drug.

Case 8.—H. L., female, aged 24. A carbuncle of the upper lip. This cleared up after treatment with 44 grm. of sulphathiazole. The blood culture was sterile. The carbuncle increased somewhat in size and the temperature remained high for several days during treatment. The carbuncle subsided without the formation of sloughs and with very little purulent discharge. The patient developed a rash resembling erythema nodosum and the white cell count fell from 21,000 per c.mm. to 6,000.

Cases 9, 10, 11.—Three cases of facial carbuncle, two of the chin and one of the temple. All three had negative blood cultures and all cleared up satisfactorily on sulphathiazole therapy.

Conclusions

Two cases only had positive blood cultures (Nos. 5 and 7). In both of these the culture remained positive whilst the patient was receiving the drug. Case 5, despite persistent pyrexia and the rheumatic mitral lesion, did not develop any metastatic abscesses or bacterial endocarditis. Case 7, despite her age and raised blood urea, recovered with the development of only a serous pleural effusion. Case 3, who was clinically a typical case of osteomyelitis, cleared up with no resulting abscess or sequestrum formation. In most of the cases, however, sulphathiazole did not appear to have influenced the local source of infection to any extent. Nos. 2 and 5 with osteomyelitis progressed to abscess

formation at the site of infection during treatment with the drug. In Nos. 7 and 8, the carbuncle increased in size during sulphathiazole administration. Blood sulphathiazole estimations suggest that large doses are necessary to achieve figures comparable with those of sulphapyridine. The employment of large doses, even in children, was not followed by any marked toxic symptoms. Vomiting was practically absent. There was a tendency to leucopenia in some of the patients, and it is probably safer to employ the drug over short periods only with frequent leucocyte counts. It is quite probable that the optimum action of the drug is obtained in the early stages of its administration.

[I wish to thank Dr. W. Allen Daley, Medical Officer of Health for the London County Council, for permission to treat the above cases.]

JOINT DISCUSSION No. 3

Section of Ophthalmology and Section of Neurology

Chairman—MALCOLM HEPBURN, F.R.C.S.
(President of Section of Ophthalmology)

[*February* 22, 1940]

DISCUSSION ON TUMOURS OF THE OPTIC NERVE

Mr. A. C. Hudson: The total number of recorded cases of primary tumours of the optic nerve and chiasma is less than 350. Most of the tumours can be classified histologically according to their origin in the glial tissue of the nerve, or in the tissues of the nerve sheath. The great majority of the sheath tumours were meningoendothelial.

The glial tumours occurred in the series in the proportion of 3 to 1 meningeal. Both types of tumour are rather commoner in the female than in the male. There is a striking difference in age-incidence. 40% of the glial tumours caused symptoms during the first five years of life, but not one meningeal. 60% of the glial tumours came to notice in the first decade, as against 24% of the meningeal; and 90% glial, as against 50% meningeal, in the first two decades.

Both types of tumour, when intra-orbital, cause exophthalmos, usually very slowly progressive. The direction of the exophthalmos is most commonly straight forwards; but sometimes it may be downwards and outwards, especially in the case of large tumours. Exophthalmos has been associated with pain in some of the meningeal tumours, and with slowly increasing hypermetropia in one case of each type of tumour.

Movements of the eyeball are often little or not at all affected by a glial tumour, a point first noticed by v. Graefe as indicative of freedom from tumour formation of the most anterior part of the nerve; in the case of meningeal tumours on the other hand limitation of movement is common, and may be complete in advanced cases, the eyeball being fixed to the cup-like anterior surface of the tumour.

Progressive defect of vision, or amaurosis, of the prominent eye is almost invariably found with both types of tumour. It has preceded exophthalmos in many cases of glial tumour, in one case by as much as twenty-four years. In the case of meningeal tumours on the other hand the failure of vision is usually explicable as the direct result of pressure of the tumour. Amaurosis, or defective vision with hemianopic field, in the prominent eye, associated with hemianopic field, and usually defective central vision, in the other, is evidence of extension of a glial tumour to the chiasma; a similar affection without exophthalmos is met with in cases in which the intracranial portion of the nerve and the chiasma are affected.

Ophthalmoscopic examination usually reveals optic atrophy or, less commonly, papilloedema. In two cases extension of a glial tumour to the nerve head has been discovered with the ophthalmoscope, and in two cases it has been found post mortem. In view of the fact that meningeal tumours not infrequently extend through the sclerotic to the choroid it is remarkable that no corresponding fundus change has been noted.

Skiagrams may show the shadow of an intra-orbital tumour. Extension of a glial tumour backwards beyond the apex of the orbit is frequently indicated by enlargement of the optic foramen. Martin and Cushing have pointed out that, with glial tumours of the chiasma and intracranial portion of the optic nerves, the sella turcica may have a gourd-shaped outline, attributable to enlargement of the optic foramina and forward extension of the sella under the anterior clinoid processes.

Prognosis.—As regards the glial tumours it is a remarkable fact that, in spite of the high percentage of cases in which removal of an orbital tumour has been complete, in only one case (Seefelder, 1931) has a recurrence of the tumour in the orbit been recorded, while subjects of incomplete operation have been found free from recurrence ten and a half and twenty years later. In other cases there has been no recurrence fifteen, eighteen and a half, nineteen, and twenty-four years (two cases) after operation.

Meningeal tumours recurred in 15% of cases, at periods from two months to twenty-five years after operation. The tumour recurring after two months was removed, and had not recurred again after two years, while another tumour, which recurred after seven months

and was removed, recurred again after nine years. A liability to recurrence is not surprising when it is borne in mind that these tumours have not infrequently been found to have invaded neighbouring structures, six times the sclerotic and the choroid, three times muscle, and once the optic nerve head.

As to expectation of life the data available are too scanty to be of much value, except in so far as they indicate the gravity of signs of involvement of the chiasma by a glial tumour. In all of the 13 cases in which death occurred under observation (at periods of one month to four years after the patient first came under notice), and in the three cases in which it occurred immediately after operation, there were symptoms of chiasmal or other intracranial disease.

Many years ago I suggested that certain peculiar features in cases of glial tumour—history of defective sight before the appearance of signs of tumour, often of many years standing, and sometimes dating from the first few months of life; absence of recurrence of tumour in the orbit after incomplete removal, and the ill-defined transition of the tumour tissue through tissue showing neuroglial proliferation into normal tissue, in spite of the absence of malignant characteristics—might be explained on the supposition that the tumours were manifestations of an overgrowth of neuroglia in tissues which had previously been exposed to some deleterious influence, and were therefore not true neoplasms, but manifestations of a degenerative gliomatosis.

Verhoeff, in 1932,[1] expressed the opinion that the tumours were true gliomas composed of cells derived from astrocytes; at the same time he made the following comment: "It may be of considerable practical importance that within the nerve-stem the growth does not advance by invading the original structure, but by causing the pre-existing neuroglia in the vicinity of the tumour to proliferate and take on the character of the tumour tissue. This would seem to indicate that some substance is produced by the tumour which stimulates the contiguous neuroglia. The possible practical importance of this observation lies in its indication that removal of the largest part of the tumour may do away with the assumed stimulating substance, and thus prevent further extension of the growth." It appears to me that this conception would place the tumours in quite a different category from true neoplasms.

The histological researches of Lundberg, inspired by the pioneer work of del Rio-Hortega, and reported in 1935 in a valuable monograph, showed that of the nine glial tumours examined all were oligodendrocytomas. No indication is given that he regarded the tumours otherwise than as true neoplasms arising in previously healthy tissue.

The evidence as to the relationship of v. Recklinghausen's disease and glial tumour of the optic nerve and chiasma, which was first adduced by Goldmann in 1893, has since then been strongly reinforced by the discovery of a considerable number of cases in which both affections were manifested in the same individual. An association of meningeal tumour with neurofibromatosis has also been met with in a few cases. A conception of glial tumour formation as analogous to the phenomenon in neurofibromatosis of a true neoplasm arising in previously abnormal tissue would accord with the clinical picture.

Dr. del Rio-Hortega (*Abstract*): The paper deals with those tumours of the optic nerve which develop in its own parenchyma and derive from its own cells. Tumours arising in the nerve sheaths, those which infiltrate the optic nerve from adjacent structures, for example, the retina, and metastatic tumours are excluded.

The old classification as sarcomas, myxosarcomas or gliosarcomas has been abandoned. The modern denominations of polar spongioblastomas and schwannoid oligodendrocytomas are not yet definite.

These tumours are certainly gliomas, similar to the cerebral gliomas, but they have a special picture. They are formed by very elongated cells arranged in bundles and plexuses. These cells are commonly bipolar, but they may have three and more processes though this astrocytic type is very rare. Among them are often small rounded cells similar to oligodendrocytes.

The interpretation of these cells is rather difficult. They could be considered atypical astroblasts, since among them there are some astrocytes which may indicate a progress in the differentiation. They could be interpreted, too, as atypical schwannoid oligodendrocytes, since among them there are other types of oligodendrocytes. But it is impossible to interpret them as polar spongioblasts without providing an artificial solution for a problem that is not yet solved.

[1] In Penfield's "Cytology and Cellular Pathology of the Nervous System".

Therefore, the denomination of these tumours may be *longicellular astroblastoma*, or *schwannoid oligodendrocytoma*. Their cells have no spongioblastic characters. They are elements in a degree of differentiation corresponding to the astroblasts and astrocytes, but morphologically they are more similar to the schwannoid oligodendrocytes.

From the differentiation of their cells it is possible to conclude that tumours of the optic nerve belong to a group comprising : (1) Tumours of the optic nerve. (2) Tumours of the optic chiasma. (3) Many tumours of the corpus callosum. (4) Many tumours of the medulla oblongata. (5) Cerebellar astrocytoma.

These tumours are morphologically linked without interruption. All these tumours have abundant bipolar, elongated cells, associated with more or less abundant astrocytes poor in processes. Clinically they all have a moderate malignancy.

[Dr. del Rio-Hortega demonstrated a series of photomicrographs illustrating his paper. It is hoped to publish his contribution in full at a later date.]

Mr. E. Wolff : Hudson (1912) in his classical paper was the first to raise his voice in protest against the usual classification of these tumours into intra- and extradural. Verhoeff (1922) in an admirable contribution entitled " Primary Intraneural Tumours (Gliomas) of the Optic Nerve " gave further evidence why the above method of describing these growths would not do. My contribution to-day will be mainly to point out certain aspects of the pathological anatomy of these tumours and to try and show how this determines their method of spread. In order to do this I have found it indispensable to compare them with their intracranial counterparts.

According to MacCallum (1936) gliomata of the brain are rarely sharply outlined either by their colour or their consistence, but shade off insensibly into the surrounding brain substance. Their position can be made out in the cut surface fairly well, however, by the swelling, the increased vascularity and translucence and by the hæmorrhages and necroses which are usually present. There are some forms, indeed, which are so diffused through the brain substance that it is difficult to determine their outline even with a microscope. Gliomata do not as a rule extend to the surface of the brain and never pierce the meninges.

Under the microscope most gliomata present a fairly uniform mass of cells rather small in size with numerous protoplasmic processes which join in a tangle with those of other cells and thus produce a network of delicate filaments. Great variety is seen in the form and arrangement of these cells. They are frequently found to have a rather abundant cytoplasm with many long processes extending in all directions so that they have acquired the name of astrocyte or spider cell. Others are much simpler in outline and they have very few prolongations. In many gliomata they are especially condensed around the blood-vessels, in others there are minute spaces about which cells are arranged radially with a flat or curved foot at the edge of the space and a long frayed-out cell body extending peripherally to become entangled with the other cells.

Degenerative changes, hæmorrhages and necroses are frequent in these tumours. They may lead to such widespread destruction of the tumour that only a thin rim of tumour tissue is left. It is not infrequent in such cases to find that the debris of the tumour cells and blood has been replaced by a clear fluid, so that the whole area appears as a thin-walled cyst with only some pigment and traces of tumour tissue in its walls to indicate its original nature.

Trotter (1918) states that the glioma is a true tumour of the brain substance and possibly the only one. Cushing and his associates have shown that the differentiation between glioma and sarcoma may be extremely difficult and that the more thorough the histological examination the fewer appear to be the cases of true primary sarcoma of the brain. There are also general grounds for supposing that true sarcoma is unlikely to arise in the brain substance. It may certainly be said that glioma must be regarded as the classical brain-substance tumour and that cases of supposed sarcoma should be regarded with caution.

A striking characteristic of all gliomas is their very slight tendency to invade non-neural tissues.

Dural endothelioma spreads on both aspects of the dura. Internally it presses on the brain in which it may make a large and deep impression but without, until the latest stages, becoming fixed to the brain substance.

The changes described are exactly like those which occur in the optic nerve tumours. It thus becomes clear that since the optic nerve is no nerve at all but a part of the brain its tumours will be, in all essential features, identical with those of the brain, and just as there is really only one brain tumour, the glioma, so there is only one intraneural tumour

of the optic nerve—also the glioma. The endothelioma in both cases is a tumour of the meninges.

The differences in the manner of growth between the intracranial glioma and endothelioma and those of the optic nerve are due to anatomical differences and especially to the arrangement of the non-neural tissues. The glioma of the optic nerve usually starts some 10 mm. behind the globe in the region where the arteria centralis enters, and it seems to me extremely likely that the profound changes that take place when the mesodermal central artery is enclosed in the backward extension of the choroidal cleft may have an important bearing on this site of election for the origin of these tumours. From this point the tumour tends to grow towards the brain so that that part between it and the eye tends to be free from growth. The reason for this is that, as stated before, the growth has little tendency to invade non-neural tissues, for anteriorly we have the arteria centralis with its connective tissue sheath and also the much denser septa present in this anterior part of the nerve. These naturally do not form an absolute barrier, for occasionally cases have been reported where the growth has reached the papilla.

The next point that calls for explanation is the presence of the growth in the subarachnoid space. Why does it get through the pia and not through the dura which is made of the same tissue? The answer appears to lie in the fact that hundreds of processes, the septa, pass from the pia into the nerve, and also in the structure of the septa themselves. A cross section of the optic nerve reveals that a number of the connective tissue septa are "incomplete", and it is probable that the growth gets into the septa at these gaps. The growth separates the constituent fibrils of the septa and so produces a characteristic appearance: in a low-power view of a cross section of the nerve at an early stage of the growth it does not appear grossly altered. The septa merely appear widened as do the enclosed spaces between them. Proceeding peripherally along the septa the growth reaches the pia whose constituent fibrillæ are also separated by the growth. The pia, however, although widened by the tumour can usually be made out separating the intra- and extra-pial portions of the growth.

As stated before the growth does not get outside the dura, and this has an important bearing on the difference between the clinical features of the glioma and the endothelioma.

The dural endothelioma of the optic nerve, like that of the central nervous system, spreads on both sides of the dura. Internally it will press on the optic nerve which may be compressed to a thread but is not invaded by the growth except perhaps at the latest stages. Externally, not being in contact with bone, it does not produce those remarkable changes in the walls of the orbit so characteristic of the changes produced in the skull by the intracranial dural endothelioma. In fact it grows freely in the orbit till, eventually, it will have the shape of the muscular cone. Anteriorly it grows round the back of the globe, pressing on it and causing an artificial hypermetropia. Also it will eventually form a cup for the back of the eye and, continuing its growth forwards, may be palpated through the eyelids. Incidentally the endothelioma is much more likely to interfere with the ciliary vessels and so produce those pigmentary changes in the fundus (as shown in a case of Sir John Parsons and published by Neame and myself, 1925) which Wagenmann and others have described after cutting these vessels experimentally in the rabbit.

Intra-ocular extension is rare both in glioma and endothelioma. But in the former the spread is along the optic nerve to the papilla, while in the latter it is through a canal for a posterior ciliary artery or nerve, so that the swelling inside the eye resulting from the tumour is peripapillary. The swelling of the disc which so often accompanies endothelioma of the optic nerve is therefore not due to the intra-ocular extension of the growth as it may be in the glioma, but to a papillœdema the result of interference with the venous or lymph drainage.

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Professor Geoffrey Jefferson said neither in the case of meningeal tumours nor in that of intrinsic glial tumours of the optic nerve could one say that the intra-orbital portion was the only part involved by the tumour. One spoke of meningioma of the optic sheath; surely such a tumour might be expected to be found only where that

sheath existed, that is, within the orbit, and in the main that was true. On the other hand, a meningioma centred on the anterior clinoid process or about the sphenoidal wing might seed itself into the optic sheath and produce there the effect of a sheath meningioma. Thus there might always be a doubt concerning a sheath meningioma as an isolated process. It might be part of a larger, perhaps undisclosed, tumour, and this might be the explanation if a case ran a course of an unfavourable character. The link would be with the meningiomas *en plaque* and of the sphenoidal wing, but although he had seen and operated on several of these cases he had not had the opportunity of verifying the state of the optic sheath in any.

He had had more than one discussion on optic sheath tumours with Harvey Cushing, who was extremely reluctant to accept the view that a sheath meningioma did exist as a perfectly individual tumour. He showed an example of one of these meningiomas *en plaque* to illustrate the unroofing of the optic canal in the hope of saving the vision in the affected eye. He showed it for two purposes, first as an example of the type of change he was talking about, and secondly as illustrating the transfrontal approach to the orbit through its roof. The roof had been cut away and carried back so as to uncover the optic nerve. The picture of the optic nerve canal beforehand did not show any great thickening, and it seemed likely that what had happened was that the tumour had actually invaded the sheath. He showed it also because it illustrated the neurosurgeon's approach to the orbit, which he thought very much superior to the external approach, not only from the point of view of cosmetic result, but because the view and the actual approach to the tumour were better, and it was, moreover, a relatively simple operation which carried no mortality.

His next case was an example of what seemed, at present at all events, to be a pure sheath tumour. This was in a young man aged 23, who had suffered increasing loss of sight in the right eye, and had slight external strabismus and exophthalmos. The vision in his left eye was normal, and his fields were normal. The eye had that elastic feel which was rather characteristic of tumours of the optic nerve which increased the mass of the nerve and produced protrusion in a perfectly mechanical way, quite apart from any other structure or engorgement or anything else in the orbit.

The eye in this case was excised, and he discovered what an unsatisfactory method of approach the trans-palpebral or ordinary frontal approach to the orbit really was. Until the eyeball had been removed one could not tell what might be lying behind it, and it was impossible to get far enough back towards the optic foramen to make a really good removal. In this case the excision of the affected nerve surgically and pathologically left much to be desired. The tumour was a sheath meningioma of the optic nerve, and in spite of the incompleteness of the removal there had been no sign of recurrence during the five years since the eye was excised, a fact which bore out what Mr. Hudson had said about the long life of some of the meningiomas. This was one of the cases which was followed by radiography during the whole time to see whether or not there was any indication of extension of the process backwards, a development undoubtedly more common in gliomatous tumours of the nerve than in sheath meningiomas, because the gliomas more definitely passed through the optic canal than the sheath meningiomas.

The remaining cases of this series—of which there were seven—were gliomas of the optic nerve and the optic chiasma. He asked his colleagues at the Royal Eye Hospital at Manchester to look up their records and this had made possible the study of another nine cases of optic nerve tumour, about half of them in children. From what Dr. del Rio-Hortega had told them it was quite clear that there was nothing really specific about the tumour of the optic nerve. He had shown the sort of polymorphism of the optic glioma which was shaded out over a background of similarity. The tumour was always the same thing, although it might have a considerable difference of appearance. It could be duplicated in the brain-stem, the pons, and the corpus callosum.

These facts were borne out by the clinical cases. The first was the case of a girl aged 12, who was admitted to the Manchester Royal Infirmary on the medical side because she had had a fit and had fallen into the fire and burnt her hand. But in addition some weakness had been observed down the left side of her body. She was at that time an ill child. She had developed a squint at the age of 18 months. Mr. Hudson had already mentioned at what an early age these troubles might begin. At the age of 5 she was seen by an ophthalmologist who said she was blind in her right eye. The left eye at that time was normal. She went on from then to be perfectly well, went to school and was always at the top of her class, until she approached the age of 12, when she began to suffer from headaches and this

weakness down the left side of her body developed. A photograph of her hands showed a certain worm-like movement of the left hand, and this made the diagnosis of increasing interest. An X-ray view of the skull showed the undercutting of the anterior clinoid process from the sella turcica. The sella turcica was practically obliterated, and there was a "gourd-like" extension below the anterior clinoid process, which Cushing and Martin thought might be very characteristic of optic glioma. He showed an illustration in point from Cushing and Martin. In the case he was describing the optic foramen was more than double the size it should be.

Here, then, was the problem: a child of 12, lately suffering from fits and severe headaches; on examination an atrophic disc in the right eye, a choked disc in the left, with some atrophy behind it, also some numbness on the left side, and X-ray evidence of enlarged sella and enlarged optic canal. The diagnosis was a tumour of the right optic nerve extending into the chiasma, and it seemed to be certain that the origin must extend into the subthalamic region and involve the nucleus subthalamicum. That proved to be the case.

Here Professor Jefferson showed a diagram of the brain as constructed from the clinical analysis, and indicated the tumour of the optic chiasma extended backwards into the brain-stem, and furnished a complete vindication of what Dr. del Rio-Hortega had just said about the unity of these processes extending from the pons and so forth right forward into the nerve behind the globe of the eye. Histologically it was seen to be the same kind of growth as Dr. del Rio-Hortega had described.

The next case was that of a boy aged 9, who had proptosis of the right eye and typical stigmata of von Recklinghausen's disease. He had actually under his skin here and there small subcutaneous neuromata. He showed one illustration of this case in order to demonstrate that the changes of the chiasma did not necessarily reflect themselves in the way that might be imagined in the sella even when there was a massive tumour. He had hoped that it might be possible in this case to cut the nerve intracranially, but the involvement of the chiasma made that impossible. The case showed that even with a tumour of this size it was not inevitable to get any great changes in the sella itself. The tumour was a glioma.

The case following furnished rather a lesson in diagnosis. A boy, aged 12, had complained for some years of failing vision in both eyes. He had no signs whatever of von Recklinghausen's disease. The story was one of visual failure. He had bilateral optic failure and an open sella turcica with no great depression of its floor. The cause of the visual failure seemed very doubtful. For the previous five years his sight had remained about the same, and then began to get rather worse. A ventriculogram showed relatively small ventricles and quite evidently a large tumour of the optic chiasma. At operation a firm white tumour was discovered which was at first thought to overlie the optic nerve and chiasma, and preparations were made to remove it by dissection, under the impression that as it became reduced in size the optic nerves would come into view. However, after the preliminary steps had been taken it was seen that the tumour was actually in the optic chiasma, and not just pre-fixed to it but extending in the optic nerve, and he was only just prevented in time from undertaking a removal which would have left no optic apparatus at all. The effect of the biopsy was not to depress the vision very much, and five years afterwards, although his vision was not by any means good, he was still able to get about. There had been a gradual deterioration, but the case again showed the extraordinary malignant attenuation of these tumours. They were fascinating cases both clinically and pathologically. Now that their nature was known, even the biopsy which he had made in this case was an unnecessary step. He would not say that one was always certain without an operation that the patient, unless he had von Recklinghausen's disease, had a glioma of the optic nerve or chiasma. But from experience with these cases he thought they could rest assured that the pathological process extended so far inward into the actual structure of the chiasma and optic nerve that it was extremely unlikely one could do the patient any good by operation, and one might easily be tempted to an intervention which would do harm. The only occasion on which good might be done was when the tumour was localized to the intra-orbital portion of the nerve.

Dr. Beatson Hird said that he had seen five cases, two belonging to other surgeons, and three of his own which he would briefly describe.

The first case was a typical one of glioma of the orbital portion of the right optic

nerve in a girl aged 15. He first saw her in the Birmingham and Midland Eye Hospital in March 1923, when she came on account of failing sight in the right eye of several months' duration. The eye had become a little prominent, and there was marked papillœdema in that eye. The movements were perfect, and the left eye normal. The sight of the right eye was reduced to less than $\frac{6}{60}$. Measurement was made with an exophthalmometer, and the eye was found to project 17 mm. as against 13·5. The pupil reactions were normal. The X-ray view of the orbit was negative. He asked permission of the parents to explore the orbit, and was allowed to do so, but not to do more at that time. The external rectus was resected and the optic nerve examined but he could not satisfy himself then, in March 1923, that there was any definite swelling of the nerve. Slowly the eye became more prominent. It was measured for a number of months, gradually the protrusion increased and the papillœdema gave way to a marked optic atrophy, the left eye still remaining normal. By November of that year, eight months after his first observation of the case, the exophthalmometer reading gave an increase of 5 mm. over that found at the first observation. Permission was obtained to explore the orbit again and to remove the eye and the tumour if he found one. This time it was obvious that the optic nerve was very swollen right up to the back of the globe, and as the eye was blind he removed the globe and the tumour. It could be seen from the illustration [shown] that the extreme end was still very thick ; the nerve had been cut clean in two ; it was extremely difficult in that child's orbit, with the nerve so thick, to get right back to the entrance of the orbit and not cut the nerve across. He took hold of the proximal end with a strong forceps and drew it as far forward as he could so as to get round to the optic foramen. The pathological report was a glioma of the optic nerve, and that patient, although he must have left behind some intracranial portion of the nerve involved, remained absolutely free from recurrence in the orbit or any involvement of the chiasma while under periodical observation over five years. After that he lost sight of her ; she left the district, and he did not know what had happened, but from what they had been told in the present discussion it was quite likely that she was still perfectly well.

This case illustrated the method he then employed to try to get right behind the growth. He had been interested to hear of Mr. Jefferson's roof approach, and it sounded to him a very good way of getting at the optic nerve tumour and seeing the full extent of the growth.

The second case was a male aged 41, seen for the first time by him in August 1936, but he had first of all gone to the Birmingham and Midland Eye Hospital and then had been passed on to the Neurological Department of the General Hospital. He had a papillœdema, a drooping of the upper lid and some evidence of ocular paralysis on the right side. It was felt that probably, as he had developed a complete ophthalmoplegia, he had a meningioma in the region of the great wing of the sphenoid. On examination on August 7, 1936, there was some ptosis of the right eye, but only slight protrusion, almost total loss of movement except downwards, contracted field of vision with marked receding angles, and visual acuity only equivalent to counting fingers. There was no evidence of involvement of the sensory nerves of the orbit, and there was a marked feeling of resistance when the eye was pushed backwards into the orbit. The left eye was normal in all respects. On August 14, a week later, he explored the right orbit and could then feel the optic nerve right up to the globe very enlarged. The same method of removal as in the first case was performed. The whole of the optic nerve right from the very back of the globe to the optic foramen had been converted into an absolutely rigid mass of cartilaginous consistency, and for that reason one could well see why the eye could not have been moved at all. The loss of movement may have been partly paralytic, certainly a great deal of it was mechanical. When he had stripped all the muscles off he could not move the globe. He cut the nerve and took hold of the posterior part and brought it forward, dissecting with his finger around the stump right back to the optic foramen. In this case there was definite erosion of the orbital roof posteriorly. The growth was reported pathologically as an endothelioma of the optic nerve sheath. The case has been under observation for three and a half years and there has been no recurrence whatever either locally in the orbit or evidence of intracranial spread, and yet in this case the intracranial portion of the optic nerve must have been involved.

The third case was that of a married woman aged 25, who had suffered from headache

all her life but much more so during the two years before she came under observation. During the previous two months she had had symptoms of failing vision. On examination the right eye was blind and the left vision very blurred. There was considerable papill-œdema in each eye, more so on the right side, with some exudate and hæmorrhage. The pupil in the right eye did not react to light. It was quite obvious that something was involving the optic nerve on the right side intracranially, but he was not prepared to make a diagnosis of the exact cause. The X-ray report was negative. The sella was quite normal, showing none of the peculiarities described by Cushing and Martin, nor was there anything else to help in the diagnosis. Mr. F. A. R. Stammers, Surgeon to the General Hospital, exposed the optic nerve on the right side by the frontal route and a swelling was found, a tumour of the intracranial portion of the optic nerve, extending forward half an inch from the chiasma which was involved to a certain extent. A small portion was taken for examination and proved to be glioma.

Although this was all that was done the patient's headaches ceased. The left eye, which had very considerable papillœdema which greatly interfered with vision, made a gradual recovery, and the vision was practically $\frac{6}{6}$ in that eye. The disc was a little pale and the field full. But it seemed to be very remarkable that merely a temporary decompression and exploration of the nerve should have been able to do so much good. He had expressed the opinion with regard to this case that if an operation was not done quite soon the patient would be blind in both eyes. It was of great interest that such a recovery should have occurred.

He congratulated Mr. Jefferson on one of his cases in which there was such a brilliant diagnosis. It was necessary to take into account optic atrophy which might follow a papillœdema or be of primary type. There was a possibility of temporal field defect in the opposite eye. The X-ray changes not only of the pituitary fossa but also of the optic canal and the optic foramen would quite likely in a certain number of cases prove of the utmost importance in the diagnosis. These cases also appeared to have consider-able loss of vision, and, lastly, in a certain number of them would be noted various signs of the involvement of the hypothalamic region.

Mr. Humphrey Neame referred to four cases of which he had had experience during the last twenty years. One point he wanted to stress particularly was the time factor. One of his cases was a child of 1½ years with proptosis, which from the history had come on rapidly, and he was afraid of sarcoma. Over a number of weeks, however, during which he watched the case, he was not convinced that the proptosis was increasing, but he thought it wiser to remove the eye and clear out the orbit, and there proved to be a typical gliomatosis. The second case [1] an endothelioma, was interesting on account of the age of onset, which was as late as 79 years. The third case [1] was a boy of 14 when first seen. The growth was removed, but not the eyeball ; the eye was in no way useful, but he thought that in the case of a working boy the socket occupied by the eye-ball was better than the fitting of a useless glass eye. The growth went right back to the optic foramen and was not by any means completely removed. The back part of the growth had broken down into a porridge-like mass. That was in 1923 ; he saw the boy fifteen years afterwards and he was still perfectly well.

Mr. Neame then proceeded to show slides illustrating these cases. In the fourth case [2] he pointed out the position of the endothelioma, going right up to the back of the eyeball, the eyeball sitting in it as in a sort of cup, of course preventing movement completely. The picture of the glioma in the child of 1½ years showed the expansion of the optic nerve—a point which Mr. Wolff had emphasized—without the destruction of its pattern, and the extension of the growth through the pia to the outside so that the nerve was surrounded by this cellular tissue.

REFERENCES

1 NEAME, *Brit. J. Ophth.*, 1923, **7**, 210.
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Professor Geoffrey Jefferson, in replying on the discussion, said what was so interesting to pursue was the extent to which tumours of the optic nerve could be confined to the nerve in its orbital portion. If no very precise information had come forward in that discussion there had at least emerged the idea that there was certainly no *a priori* reason why a tumour should not for a time be confined to the nerve in the orbit.

Section of Odontology

President—S. F. St. J. Steadman, L.R.C.P., M.R.C.S., D.P.H., L.D.S.

[*April* 22, 1940]

Some Considerations of the Pathology and Treatment of Suppurations around the Angle of the Mandible

By C. Naylor-Strong, F.R.C.S.Eng., L.D.S.Birm.

The origin of acute inflammation in the region of the angle of the mandible may be roughly divided into three groups :—

(*a*) Those cases where a tooth is partially erupted, and some inflammation of the gum is caused by debris getting under the flaps. This forms a nidus of infection which spreads as a cellulitis to the structures around.

(*b*) Those cases which are plainly post-operative, where inflammation has taken place after apparently most careful surgical procedure.

(*c*) Those cases where suppuration has followed injections, such as mandibular ones, into that area.

The signs and symptoms of these cases differ to a marked degree, not only in severity, but also in clinical course. First there is a type where the spasm of the muscles is prolonged, early trismus is a marked feature, there is swelling in the region of the jaw, painful and tender, which becomes localized but which lasts a long time. This is followed by tenderness over the outer side of the mandible, and after the spasm has disappeared, there is still some mechanical difficulty in opening the mouth. Small pieces of dead bone, sequestra, are prone to appear, and the whole disease runs a rather chronic, but ultimately favourable course. Sometimes a sinus forms on the outside, but this, after being curetted, clears up, leaving a dry scar and a healed wound. But the course of the disease is long and tedious. Conservative treatment is the keynote, and resolution is the rule.

The second type of case is materially different from the very outset. The patients, soon after the onset, become febrile and much more ill than the local signs would seem to show, and to the experienced observer it is obvious that their articulation is at fault. It was this particular type of speech which first betrayed to me what I think is a particular type of case. The history may be identical, but the victims of this type of suppuration complain not so much of trismus, for they can open their mouths at first, but of difficulty in swallowing, of a change in voice, and of pain in the ear of the same side, with some difficulty in putting out the tongue. The pulse-rate and temperature are higher, and their illness is sudden and severe; a matter of hours compared with days in the first type.

In the first set of signs and symptoms trismus appears early, and in the second, late. And again, in the first, articulation is good but the voice is hindered by the closed mouth, whereas in the second the formation of words is impeded, and articulation is such that vowel sounds are over-accentuated and consonants are lost.

A similar type of speech to the second occurs in patients who have a condition of

suppuration around the capsule of the tonsil, or a diphtheritic paralysis of the soft palate of that side. The peculiar voice of the second type is caused by the partial immobility of the levator palati and palato-pharyngeus muscles.

One can therefore assume that although the start of the inflammatory process is the same, the products of inflammation have spread along different paths. Have we an anatomical explanation for this?

A study of the anatomy of the outer side of the mandible reveals an oblique line, above which the greater part of the area is covered by mucous membrane, and below and behind which there are muscular attachments, or the area is beneath the skin.

By far the greater portion is occupied by the masseter, and a portion in front, above and below, is occupied by the temporal muscle and the buccinator. A part of this area is covered by the muscle, and a part is attached to the muscle, and between the area covered by the muscle and the muscle itself there is a small space occupied by the parotid gland. There is also a space in front of the masseter between the temporal and the buccinator, which is covered by two thin sheets, the platysma and risorius, and crossed by the facial artery and vein: this is an area of spread of infection. There are two possible avenues of spread, one above the attachment of the masseter, between it and the bone, and another in front of that muscle, really between the lower and anterior end of the temporalis attachment and the posterior end of the buccinator. The tracking of infection along these routes is in great part the cause of the swelling, the tenderness and the trismus. This also explains why abscesses may point in the pre-auricular region, or just in front of the angle of the jaw.

When we look at the inner side of the jaw we find there is a large dividing line, the mylohyoid line, between the upper and front part, and lower and back. All swellings above this line are in the mouth, and everything below the line is in the neck. The upper and front portion is covered by mucous membrane and the sublingual gland. The lower portion houses the submaxillary and the internal pterygoid, while between the posterior end of the mylohyoid line and the internal pterygoid there is a space which allows the mylohyoid nerve and artery to pass into the neck. The lingual nerve is above and in front, the dental artery and vein are above and behind. The temporal muscle is attached with the parotid curling round the back. This side of the jaw is covered by the two pterygoids, and the vertical portion of the jaw is thus sandwiched between two sets of muscles.

It is a common occurrence for suppuration to spread upwards, backwards or downwards from this region on the inner side of the mandible. In addition to these bony and muscular planes, there are certain accessory structures which guide fluid into these channels. I refer to the internal lateral ligament of the jaw, and to the stylomandibular ligament. On the median side of the mandible there is another muscle, the superior constrictor, which acts as it were like a lining muscle covering the inside of the whole region, and separating it from the throat, tonsil, and tongue. It forms what is really the wall of the first part of the gut, if we may so term the posterior portion of the mouth, and it is easy to see how fluid tracking into the spaces on either side of the internal pterygoid or under the parotid gland may run into the fascial planes of the neck.

Besides these horizontal intermuscular and osseous spaces, there are vertical extensions of these spaces, which are of paramount importance, for vertical spread may cause as much distress as does the horizontal. Progress of the pus downwards on the outer side of the mandible is stopped by the attachment of the masseter to the bone, or by the deep fascia attached along the lower border of the jaw. If it perforates behind this, or through it, the pus appears on the skin, when it localizes early, and is comparatively harmless.

Let us now consider the track of inflammatory products vertically downwards, and upwards from the spaces on the inner side. Behind the tonsil, in the region of the pterygoids, there is a space which contains loose fibro-fatty tissue, and if this space is traced downwards it leads into the neck and into the region of the stylohyoid ligament and the stylohyoid muscles. In this region the larynx is suspended by its ligamentous structures. This is the keynote of the severity of the second type of inflammation. The lower pole of the tonsil is pushed forward, and the fluid tracks towards the opening of the air passages. Œdema of the false cords ensues, and the entrance to the larynx is threatened by closure. This space is extensive, passing right round the larynx from

side to side, and inflammation here may travel with great rapidity unimpeded, producing severe toxæmia.

If the infection travels upwards and backwards it will pass along the lateral ligament into the region of the internal maxillary artery and vein. This region contains a plexus of veins, which are in direct connexion with the intracranial vessels by virtue of the tiny veins through the foramina in the base of the skull, infection of which may produce intracranial thrombosis and its serious consequences.

It is clear, then, that suppuration on the inside of the mandible is of a totally different character and prognosis from that on the outer side, and that in order to stem the tide of advancing infection and œdema of the glottis, we must adopt a more rapid surgical treatment.

The following cases illustrate the two types of inflammation :—

A. Type I.—Case 1 : Extraction under nitrous oxide. The teeth were brittle, and some of the roots were not removed. I saw her about six weeks after this occurrence, and the history given me was that after the extractions she had a great deal of pain, and very obstinate trismus. A large swelling appeared over the outer surface of the jaw, which slowly subsided. At the end of a month she was still only able to open her jaws about an inch, and she still had pain. The sockets were septic. An X-ray taken at the time of our interview showed the retained roots, and osteitis of the mandible. I therefore felt that as this inflammation was threatening to spread from the region of these roots into the jaw, it would be better if the roots were removed. The operation gave rise to no reaction, and for a few days she remained quite well. Four days later, while she was having lunch, a pathological fracture occurred. There was almost perfect apposition, and splinting was unnecessary : I merely warned her to be careful. About a week later, ten weeks after the extractions, small splinters of bone came away on the outer side. The sepsis rapidly began to clear, and she wrote some days ago, saying that she was quite well, her jaw was quite satisfactory, and she felt no ill-effects.

This is a case of Type I, where the infection was on the outer side of the jaw, the trismus was a very marked feature, but the temperature was not raised to any extent, and there was no difficulty in swallowing, respiration or articulation. It ran a rather prolonged, but comparatively harmless course, and ended favourably.

Case 2 : A boy, aged 5, had some carious teeth, and it was noticed before they were extracted that a swelling had appeared on the outer surface of his jaw, just in front of the angle, and there was some pus round the teeth. The teeth were extracted easily, and at this time he had almost no pain, no pyrexia and little disability. He was given mouthwashes and irrigation to the sockets, and over a period of months small sequestra from the outer surface of the jaw appeared from time to time.

When I saw him nine months later he had a large swelling, extending half the length of the mandible, on its outer surface. There was a large sequestrum which consisted of nearly the whole of the outer alveolus, and pus was oozing from the region. The sequestrum was removed and for a further six months all went well. At the end of this time he returned, with a swelling pointing near the angle of the jaw, again on the outer side. Pus was just beneath the skin, and so I was forced to open externally. Later a further sequestrum appeared on the outside of the mandible, and discharged itself into the mouth, after which he recovered completely.

This is a typical case of Type I, showing the long history, the apyrexia, the trismus, and the sequestra from the outer surface. In the end they nearly all do well.

B. Type II.—Case 3 was that of a lady between 40 and 50. About ten days before I saw her she had had a carious lower 8 extracted under nitrous oxide. She had some pain afterwards, but it was not very severe until about forty-eight hours before I saw her. She then experienced a severe neuralgic pain which passed down her neck, and pain in the ear of the same side. Her temperature began to rise, and swallowing became painful. These symptoms progressed, and when I saw her she had a good deal of dysphagia, difficulty in articulation, and some trismus. She was sufficiently ill to cause grave concern to the two medical practitioners and the dental surgeon then in charge of her.

On examination I found that there was œdema over the inner side of the mandible. The lower pole of the tonsil was pushed forward and there was swelling in the lower half of the pharynx. The mucous membrane in the region of the extraction was red and angry, and the digastric gland was enlarged and painful.

After this condition had been dealt with, a second swelling appeared over the region of the zygoma of the same side, having no connexion whatever with the first. This

proved to be an abscess which I drained into the mouth by an incision in the inside. A month later a swelling appeared in the mid-line of the neck, over the isthmus of the thyroid gland. It was red and tender, but disappeared after a few days. This was thought to be an area of inflammation or infection in the thyroid, but as it was not opened there is a little doubt.

Case 4 is that of a lady in the early thirties, who seventy-two hours before I saw her, had had a molar tooth extracted under a mandibular injection. Twelve hours later she complained of slight stiffness in the jaw, and at the end of twenty-four hours she had pain on swallowing, but no swelling. At the end of the next day swelling had appeared, swallowing was impossible, talking was difficult, and the temperature was raised. She had exactly the same physical signs and the same symptoms as the previous case. An incision along the inner side of the jaw in the region of the mandibular raphe located pus, which was drained in identically the same manner.

Treatment

In treatment, particularly of the dangerous Type II where the inflammation is on the inner side of the jaw, a general anæsthetic is necessary together with every facility that the operating theatre can provide. Assuming that the case has little stridor there is no danger in the anæsthetic, but a laryngoscope should be at hand. After the patient has been anæsthetized, it is very helpful to have a Boyle Davis gag, such as is used for dissection of tonsils. This gag is put in position, but the patient has the head flat, and not in the position as used for tonsillectomy. The anæsthetic is administered either in an intratracheal tube, or a nasal catheter, and the pharynx is lightly packed. The œdematous area will then be seen quite clearly, and before any incision is made a sucker must be at hand. The post-nasal space is packed with a little gauze, and the tapes clipped. The whole operating table is then raised, and tilted so that the head is about a foot lower than the feet. An incision is then made along the inner side of the mandible, about half an inch in length, and about the same distance behind the last molar socket. A pair of right-angled aural dressing forceps make a very convenient probe, and these are passed down into the soft tissue, towards the opening of the larynx, without any resistance. Pus is easily encountered, and the small metal sucker is placed into the sinus thus made. This sucks away all the products. A small rubber tube, about the diameter of a pocket-diary pencil, is then placed into the sinus track. The upper end of the tube is fixed by a solitary catgut stitch to the mouth of this small incision, and is cut short so as not to irritate.

Immediately the patient is round, hot fomentations are applied to the neck, and prontosil is given by mouth in the usual dosage. It is advantageous for the patient to have a steam kettle containing a little friar's balsam or menthol, and a throat spray of chloretone inhalant.

These cases subside quickly under this treatment, and it is only a matter of a few days before they are out of danger, provided they are seen early.

As to the treatment of suppuration on the outer side, there is little more to add. Allowing the sequestrum to separate naturally as far as possible is the easiest course, as these cases do not give rise to great anxiety. As the sequestra on the outer surface loosen, they should be removed, and abscesses should be drained.

Section of Urology

President—JOHN EVERIDGE, O.B.E., F.R.C.S.

[*April* 25, 1940]

Fusion of the Kidneys

By J. SWIFT JOLY, F.R.C.S.

UNDER the heading of "Renal Fusion", one considers cases in which the kidneys are more or less intimately united into a single mass. This mass may lie across the middle line, or may be placed entirely to one side of it. Thus one speaks of "symmetrical" or "median" fusion in contradistinction to "unsymmetrical" or "lateral" union. Each one of these types is further subdivided according to the appearance of the resulting mass, and the terms "clump-shaped kidney", "cake-shaped kidney", "*rein en galette*", "*kuchenniere*", "horseshoe kidney", "sigmoid kidney", "long kidney", &c., are in common use. They have the disadvantage that they do not give any real indication as to the type of the fusion, or the period of fœtal life in which the anomaly arose. In addition they are often confusing, as the same descriptive term may be applied to quite different anomalies. For example, the term "*kuchenniere*" is used to describe cases in which single unfused kidneys have failed to rotate during their ascent from the pelvis to the lumbar fossa, as well as those in which the "cake-like" mass results from the fusion of the two kidneys. I suggest, therefore, that this nomenclature should be completely abandoned, and that one depending on the nature and extent of the fusion should be substituted for it.

Classification.—The classification I suggest is as follows:—

(1) Complete fusion.

(2) Incomplete fusion. (This always takes place at the poles.)

(*a*) Fusion of similar poles.

(*b*) Fusion of dissimilar poles.

This simple classification embraces all forms of renal fusion. In cases of complete fusion, the united mass shows little or no evidence that it originally arose from the union of two distinct organs. It either forms an irregular mass, or it may be roughly quadrilateral in shape, resembling a ship's biscuit, from which is derived the name "*rein en galette*". When similar poles are fused, we have a horseshoe kidney. The ordinary form of this anomaly results from the fusion of both lower poles, while the "reversed" form is brought about by the fusion of the upper poles. Fusion of dissimilar poles gives rise to the various forms of "long" kidney. Such an organ usually, though not always, lies completely to one side of the middle line, and comprises cases described as lateral fusion in the older nomenclature.

(1) COMPLETE FUSION

The renal mass resulting from the complete fusion of the two developing kidneys is variable both in shape and position. The most common form is a quadrilateral organ, with well-rounded corners. It is flattened from before backwards, and may occasionally show a notch on its upper or lower border, indicating the point of fusion. This type rather resembles a ship's biscuit, and to it the name "*rein en galette*" properly belongs. A second type is that of a round oval organ, which does not show any indication that

it arose from two separate organs. Its surface is generally smooth, and free from notches and furrows. In the third type, the surface of the renal mass is markedly irregular. Its surface is lobulated, and the lobules are separated by deep grooves in which the blood-vessels and ureters lie. These lobules have no relationship to the fœtal lobulation of the kidney. They are irregular portions of the parenchyma, separated from each other by the blood-vessels. The grooves are simply due to the pressure of these vessels.

These kidneys are always ectopic. They never rise above the level of the 4th or 5th lumbar vertebra. Most of them lie in the true pelvis, but some rest on the pelvic brim. In most instances they are symmetrically placed regarding the middle line, but occasionally the greater part of the organ lies to one side of it. In all cases, however, the median plane cuts through some portion of the kidney.

The clearest indication that these organs arise from the fusion of the two kidneys lies in the fact that they always have two renal pelves. They are situated on the anterior surface of the organ, at some distance from each other, and never communicate. The ureters open normally at the angles of the trigone.

The blood supply is always irregular. The kidney mass is supplied by several arteries which arise from the aorta, the common or internal iliacs, or from branches of the latter, such as the uterine.

Embryology.—The permanent kidneys have a double origin. The excretory part arises from an oval mass of condensed mesenchyme, the cells of which are derived from the caudal part of the nephrogenic cord. The ureter, renal pelvis, calyces and collecting tubules, in other words the drainage system of the kidney, is derived from a hollow bud, which arises from the posterior aspect of the Wolffian duct, just before it opens into the cloaca. This bud grows backwards until it meets the mass of nephrogenic tissue mentioned above. From the union of these two elements the permanent kidney is formed. It is unnecessary here to go into the complicated process of development of the kidney; all that need be described is the migration of the developing kidney from the pelvis to its permanent position.

The two oval masses of nephrogenic tissue lie at first in the posterior part of the pelvis, at a level which will ultimately become the level of the 2nd sacral vertebra. They lie close together, with their long axes directed cranially and slightly laterally. This means that the caudal poles are closer to each other than any other portion. The proximal extremities of the ureteric buds become dilated in a vertical direction, the first indication of the renal pelves, and come in contact with the middle of the anterior surfaces of the nephrogenic masses. The kidneys first ascend along the posterior wall of the pelvis, each on its own side of the mesentery of the hind-gut. When they reach the brim of the pelvis, they begin to rotate as well as to ascend. Each kidney turns inwards through approximately a right angle, so that the renal pelvis instead of lying anteriorly, takes up a position in its inner border.

The changes in the arterial supply of the kidney during its ascent are of interest, and also serve as an indication of the extent of its vertical movement. A series of transverse branches are given off from the aorta and the primitive iliacs to supply the mesonephros. These are roughly, though not absolutely, segmental. As a rule each artery supplies one segment of the mesonephros, but occasionally one segment may be supplied by two arteries, or else two contiguous segments may be supplied by a single vessel. When the permanent kidney commences its ascent, it comes into contact with the lowermost of these arteries, and for a time derives its blood supply from them. As it ascends higher, it comes into contact with fresh vessels above, while it loses its connexion with those below. Viewed from this aspect, the ascent of the kidney has been compared to the action of a man climbing a ladder. His hands continually grasp higher and higher rungs, while as he steps upwards he loses contact with the lower ones. At the same time, the number of rungs between the position of his hands and feet remains fairly constant.

The amount by which a kidney ascends can be determined not only by its ultimate position relative to the vertebral column, but also, though less accurately, by its failure to rotate, or by anomalies in its vascular supply. A kidney that has not reached the top of the ladder is liable to be abnormal in both these respects.

In cases of complete renal fusion there is no indication of rotation. This is shown by the fact that both renal pelves are placed anteriorly, and at some distance from each

other. If each of the two components out of which it was originally formed had commenced to rotate before the fusion took place, one would expect that the two renal pelves would be close to each other, if not actually touching. Again, the arteries supplying such an organ arise from the lower end of the aorta, the common or internal iliacs, or from some of the pelvic visceral vessels. Both these facts confirm the supposition that fusion must have taken place in a very early stage of development, before the organs had left their primitive position.

This gives a clue to the reason why the fused mass is always ectopic. Normal unfused kidneys can slip upwards with comparative freedom through the undifferentiated mesenchyme of the posterior abdominal wall, and in their ascent they pass one on either side of the mesentery of the hind-gut. When fusion takes place, the kidneys unite behind the lower portion of the gut. The fused mass can then only ascend by forcing its way through the base of the mesentery, which obviously offers a much greater resistance. In many cases it forms an unsurmountable barrier, and the renal mass remains permanently in the hollow of the sacrum. In others, a limited amount of ascent takes place, but the upper border of the kidney mass never rises above the lower border of the 4th lumbar vertebra. Further ascent is stopped by the inferior mesenteric artery. This artery is the primitive artery of the hind-gut, and is formed before the kidney commences its ascent. In every case where the kidneys are fused across the middle line, it forms a barrier which cannot be passed. As far as I know, the importance of this artery in preventing the full ascent of fused kidneys has not been previously stressed. This applies not only to cases of complete fusion, but also to those of the ordinary type of horseshoe kidney.

(2) Incomplete Fusion

(*a*) *Fusion of Similar Poles. The Horseshoe Kidney*

In practically all cases of partial fusion, the kidneys are united by their poles. When similar poles, i.e. both lower or both upper poles, are united one obtains the horseshoe kidney. When the upper pole of one kidney becomes united to the lower pole of the other, the resulting mass is usually called the "long kidney", or else it is said to be a case of "lateral fusion". This term does not mean that the kidneys are united laterally, but that the mass resulting from the fusion of dissimilar poles usually lies entirely to one side of the middle line. It is thus not entirely free from ambiguity.

Fusion of both lower poles.—This is the ordinary type of horseshoe kidney, and is one of the most common renal anomalies. According to post-mortem statistics it occurs once in every 750 individuals, but there is no doubt that it is much more common clinically than this figure would suggest. Judd, Braasch, and Scholl [1] note that a horseshoe kidney was found 17 times in the course of 2,424 kidney operations. Botez [2] records 7 cases in 1,000 renal operations performed by Israel and Marion. Both these statements agree in that the anomaly occurs once in every 143 operations on the kidney. One must, therefore, conclude that horseshoe kidneys are much more prone to disease than normal organs.

The horseshoe kidney consists of three parts, the two lateral masses and the isthmus. In a few instances the isthmus is wanting, in which case the lateral masses are fused together at their lower extremities. When this happens, the gap between them is V-shaped. As a rule, the lateral masses are united by an isthmus or bridge of tissue, which is generally 2 to 2½ in. (5 to 6 cm.) in length. The gap between the renal masses is then U-shaped. The isthmus is usually composed of kidney tissue. Occasionally it is thick and bulky, resembling a third kidney lying horizontally. Its most common form is that of a strap-like mass, flattened from before backwards, and with sharp upper and lower borders. In a few instances it does not contain any renal tissue, and is then a fibrous band or cord, derived from the true capsule of the kidneys it unites.

As a rule, the isthmus crosses the middle line at the level of the 4th lumbar vertebra. It then crosses the bifurcation of the aorta, and a small portion of the vessel above this point, but it always lies below the origin of the inferior mesenteric artery. This vessel may arise as much as an inch above its upper border, but as a rule the relationship is much more intimate, and it either touches the upper border of the isthmus, or it may notch it close to its junction with the left lateral mass. One must always be on the

look-out for this artery when removing the left half of a horseshoe kidney. Although the relationship of the isthmus to the inferior mesenteric artery has been noted by many observers, I can find no record in which it is stated that it forms an impassable barrier to the further ascent of the fused organ. It is to my mind the principal reason why horseshoe kidneys usually lie well below the normal position.

The lateral masses are usually equal in size, but there are many exceptions to this statement. The size of one mass may be altered by disease, or the inequality may be congenital. When the isthmus is bulky it may be formed almost entirely from one kidney, with the result that the fused organ is asymmetrical. In other cases one-half may be hypoplastic. The whole kidney mass then assumes the appearance of the letter L. These L-shaped kidneys have been described as intermediate forms between the horseshoe and the long kidney, but I cannot agree with this conception, as I consider that these two anomalies arise in an entirely different manner.

Each lateral mass is either bean-shaped or ovoid. The lower poles are closer together than the upper. This means that the long axis of each mass is directed from below upwards and outwards. The upper pole usually lies about the level of the lower border of the 1st lumbar vertebra, and the lower pole occupies a position about the level of the upper border of the 5th lumbar vertebra. This position is variable, but the whole organ is usually abdominal, and in pyelograms the tip of the upper calyx lies well below the last rib. The anterior surface of each lateral mass may show grooves in which the ureters and the spermatic vessel lie. The root of the mesentery may form an oblique groove in the lower pole of the right lateral mass, while as I have already stated, the inferior mesenteric artery may notch the isthmus on the left side.

One renal pelvis lies on the anterior aspect of each lateral mass. It may follow the long axis of the mass, in which case it is directed from below upwards and outwards. The calyces then lie alternately on its inner and outer sides, and the whole arrangement resembles a compound leaf. This form of renal pelvis is only observed when there is absolutely no internal rotation of the kidney mass, and is not very common.

In a second variety, the renal pelvis appears to lie obliquely across the anterior surface of the kidney. Its lower extremity is placed approximately half-way between the inner and outer borders, while the upper end lies on the inner border. In such cases, the upper calyces are all directed outwards, while some of the lower point inwards. This arrangement is brought about by internal rotation of the upper portion of the kidney mass, while the lower part is prevented from rotating by its connexion with the isthmus. The kidney is then twisted spirally round its long axis, the upper pole being rotated inward through a right angle. This arrangement gives a very characteristic pyelogram, but it is not very common. In the third, and most common variety, one finds a lower calyx on one or both sides, projecting horizontally inwards, and penetrating into the isthmus. If such a calyx is present on both sides, their tips may only be one or two centimetres apart. If only one-half of the isthmus is penetrated by a calyx, its tip may reach almost to the middle line. The presence of calyces draining one or both sides of the isthmus is, of course, absolutely typical of a horseshoe kidney.

Most cases of horseshoe kidney are now diagnosed by means of pyelography. The most important diagnostic points are : (1) The course of the lumbar portion of the ureter is directed outwards as well as upwards. Gutierrez [3] first described this appearance, which he called the "flower-vase figure of the ureters". The bowl of the vase is formed by the deep curves of the pelvic portions, while the "wide flaring mouth" is formed by their course upwards and outwards to their respective renal pelves. (2) The presence of an inwardly pointing calyx which drains the isthmus. This may be present on one or both sides. (3) The shadow thrown by the opaque fluid in the renal pelvis may be fusiform. Its long axis continues the course of the ureters, that is, it is directed upwards and outwards, and the calyces are directed both inwards and outwards. This arrangement is found only when the lateral masses have failed to rotate. (4) When the upper poles have rotated, the upper portion of the pyelographic shadow appears to be normal. The upper calyces are all directed outwards, while some, at least, of the lower pass inwards. In such cases the shadow of the renal pelvis is almost vertical. (5) The pyelographic shadow may be intermediate between (3) and (4). Some of the calyces from both poles of the kidney look inwards, while others extend outwards. (6) The whole pyelographic shadow lies well below that of the last rib. This is an indication that the fused kidney lies at a lower level than usual.

The arterial supply of horseshoe kidneys has been studied by Papin [4], and it is only necessary to summarize his conclusions. He collected 127 cases from the literature in which accurate information had been given on this point. He found that one artery was present in one case, two in 26 cases, three in 40, four in 25, five in 20, six in 9, while seven, eight and ten arteries were found in two cases. When two arteries were present, each arose from the aorta usually at a point well below the normal origin of the renal arteries, and each supplied one lateral mass. In cases where three were found, the isthmus usually received an independent supply. The third artery usually arose from the aorta just above the isthmus, but in a few instances it lay below it, taking its origin either from the aorta, one of the common iliacs, or the middle sacral. When four arteries were present, each lateral mass usually received two, but occasionally there were two vessels supplying one side, and one the other, while the isthmus received the fourth. When five, or more, arteries were noted, the distribution was so variable that classification became impossible. All that one can say is the more numerous the arteries, the greater the tendency for some of them to arise from vessels other than the aorta. A second point is that irregularity in the arterial supply is an additional indication that the renal mass has not risen to its normal level, but is always more or less ectopic.

Embryology.—I think there can be no doubt that in this type of renal fusion the kidneys become united in an exceedingly early stage of their development. The two oval masses of nephrogenic tissue at first lie in the posterior part of the pelvis, with their caudal extremities almost touching. It does not need more than the slightest amount of displacement to make them touch and fuse. At first there could be no true isthmus, as the contact is direct, and not through the presence of a third medianly placed mass of nephrogenic tissue. This means that the gap between the masses is V-shaped, and it may be noticed that this type of gap occasionally persists. Now, as the fused kidney mass commences its ascent, the resistance of the mesentery is directed entirely against the apex of the V. As the point of fusion is comparatively small in these cases, it can force its way through the tissues of the mesentery comparatively easily, and consequently the kidney mass rises to a higher level than is usual in cases of complete fusion. It cannot, however, rise to the normal level reached by unfused kidneys, as the inferior mesenteric artery prevents further progress. One thus finds that the isthmus usually lies across the lower extremities of the great vessels, with the inferior mesenteric in more or less intimate relationship with its upper border.

One must remember that the fœtal mesentery differs greatly from the adult. In the first place, it extends throughout the whole length of the gut, and lies mesially. In the second, it is much thicker in comparison with the lumen of the gut than in the adult, and contains a fair amount of tissue, which is more condensed than the subperitoneal tissue on either side of it. A greater resistance is thus encountered by a fused kidney in its ascent, than by the two unfused organs.

Although one does not know the factors which bring about the ascent of the kidneys, it is obvious that they must exert a considerable amount of force on the developing organs. The ascent cannot be brought about by the pull of the blood-vessels on the kidney, as it climbs from one to the other during its ascent. It may be that the lower end of the mesonephros as it atrophies pulls on the permanent kidney, and drags it out of the pelvis. The metanephros is developed from the lower end of the nephrogenic cord, and in the earlier stages, at all events, a band of cellular tissue can be seen connecting it with the lower end of the mesonephros. In any case, one must not measure the amount of ascent of the permanent kidney by the length of the ureter. By far the greater part of the length of this tube is due to the growth that takes place in the lower lumbar region of the fœtus. Still, one cannot account for the fact that the kidney rises out of the pelvis, except under the urge of some force at present little understood.

The formation of the isthmus still remains to be explained. When the two masses of nephrogenic tissue unite there is no isthmus, unless one postulates that in cases of fusion of the lower poles, a third mass of this tissue lies between them. This possibility is not likely, and is not mentioned in any work on the embryology I have consulted. The formation of the isthmus can, however, be explained mechanically. If we suppose that the developing kidneys become united before ascent commences, it is obvious that the resistance of the mesentery falls chiefly on the point of union. It is, as it were, caught down by a hook, while the kidney masses on either side are pulled

upwards. This traction tends to stretch the junction between the lateral masses, so that they no longer lie in contact, but are separated by a band of tissue. Usually this band contains kidney tissue, and forms the parenchymatous isthmus, but occasionally it may be formed solely of fibrous tissue derived from the capsule of the two lateral masses. When a parenchymatous isthmus does not contain a calyx, it is entirely composed of tissue derived from the cortex of both lateral masses, but when it is drained by a special calyx medullary tissue is also present. The formation of a calyx draining the isthmus is thus due to traction, and in fact it is simply a lower minor calyx which has become displaced into the isthmus. Its formation may be compared with the formation of a traction diverticulum in any other hollow organ. Support of this theory is given by the fact that this calyx is unusually long. When the developing kidney mass rises out of the pelvis, the two lateral masses are separated by the projection of the vertebral column. The tension on the isthmus is thus kept up. This point can be observed during operation, as when the isthmus is divided, the free ends retract and become widely separated from each other.

Fusion of both upper poles.—This condition is sometimes called the "reversed horseshoe kidney", or the "horseshoe kidney with the concavity looking downwards". It is a very rare condition, and it is interesting to note that it appears to be less common now than was formerly thought. In 1911, Botez [5] collected 184 cases of horseshoe kidney in which the anomaly was discovered on post-mortem examination. Out of 88 which were published before the end of 1880, five were described as having the concavity looking downwards, while out of 96 cases published since that date, only one was so described. One must conclude from these figures, that either some of the earlier descriptions were inaccurate, or else that the condition is becoming rarer. The latter supposition is difficult to maintain, as we are dealing with a congenital anomaly, and not with a disease. One cannot think that some change is taking place, or has taken place, in the development of the kidney, which reduces the likelihood of upper pole fusion. Gruber [6] is sceptical about the accuracy of some of the earlier cases, which he apparently thinks were mounted upside down, and were really examples of the ordinary horseshoe kidney.

Twenty cases of this form of horseshoe kidney have been described. Unfortunately I have only been able to consult the original publications in a small number. Even in some of these, the description is so imperfect that it is difficult to decide on the nature of the anomaly. Still it is certain that a few cases of true upper pole fusion do exist.

The most detailed description of a case of this nature was given by Kelly and Burnham [7] in 1915. It occurred in a stillborn female. A spina bifida and an enormous left-sided diaphragmatic hernia were also present. "The great abdominal vessels were drawn considerably in a ventral direction, owing to the traction of the cœliac axis and superior mesenteric artery, caused by the intestines lodged in the left pleural cavity." The isthmus connecting the upper poles of the kidneys lay behind the great vessels, and the suprarenal bodies were also fused across the middle line. The authors are of the opinion that the kidneys must have become fused after they had ascended out of the pelvis. This opinion is supported by the fact that the suprarenal bodies were also united.

Gutierrez [8] described an interesting example, discovered during the post-mortem examination in a female aged 50. The exact cause of death was not determined. "The specimen represented the very rare instance of renal fusion made near the upper pole by a true isthmus of renal parenchyma, lying in front of and across the great abdominal vessels. The pelves are of intrarenal type and are anteriorly situated. . . . The two ureters open normally into the bladder." The right renal mass was lower than the left, "but otherwise fairly normal in position". The illustration of this specimen showed both lateral masses to be approximately at the same level, if anything the right was slightly higher than the left. The left kidney mass was disc-shaped, while the right was distinctly oval. The upper pole of the left mass was united to the right at about the junction of its middle and upper thirds, so that there was a shallow notch above the isthmus, and a very deep one below it. The isthmus was very short, and the lateral masses lay almost in contact. The relationship of the isthmus to the anterior branches of the aorta was not given.

Gordon-Taylor [9] appears to be the only surgeon to have operated on a kidney of this type. His patient had a calculus in the left renal pelvis. A paravertebral incision was made, but the kidney could not be brought up to the surface, as the inner border of its upper pole was fixed in the depths of the wound. An anterior pyelolithotomy was performed. Nine years later the patient had a recurrence of the stone. On this occasion an oblique incision was made. The upper pole of the kidney was found to be attached to a broad band of apparently renal tissue stretching across the middle line. From pyelograms subsequently made, Gordon-Taylor came to the conclusion that he was dealing with a true case of upper pole fusion.

Thompson [10] briefly reported two cases from the post-mortem records of Guy's Hospital. They are as follows :—

1075. Male, aged 6 weeks. Death from syphilis and bronchopneumonia. The kidneys were joined at their upper extremities. The kidney mass lay in the mid-lumbar region.

1531. Female, aged 15 years. Orthopædic case. Cuneiform osteotomy had been performed on femora and radii. Suppression of urine. Horseshoe kidney with the convexity directed upwards. Two ureters. Mass lay opposite 3rd and 4th lumbar vertebræ. Vessels normal. Chronic interstitial nephritis.

Unfortunately, neither of these specimens is in the Guy's Hospital Museum, nor is there a specimen of upper pole fusion in the Hunterian Museum.

These are all the cases I have found in the literature of the last twenty-five years. They show that the anomaly does occur, but they shed little light on the mechanism by which it is brought about. In Kelly's case fusion probably took place after the kidneys had risen out of the pelvis. This is important as it tends to indicate that the kidneys can fuse if they are brought into apposition in a comparatively large stage of development. There is no evidence in any of the other cases I have mentioned to show whether fusion occurred before or after the ascent of the kidneys. The relationship of the bridge with the inferior mesenteric artery is not mentioned in any of them. One can only speculate as to the origin of this anomaly when more cases have been accurately described.

(*b*) *Fusion of Dissimilar Poles*

Fusion of the upper pole of one kidney with the lower pole of its fellow is a rare anomaly, and according to Papin [11] only about 70 cases have been described. The resulting mass has been described as the "long kidney", the "sigmoid kidney", or the result of lateral fusion. Several varieties have been described, the chief distinction between them being the course followed by the ureter. Its course, however, depends entirely on the relative position of the two renal pelves. The position of the lower ends of the ureters is always constant, as in every case they open normally at the angles of the trigone. One feels, therefore, that if any classification is necessary it should depend more on the position of the kidney masses than on the course taken by the ureters.

As a rule, this form of fusion results in a sausage-shaped renal mass, which is slightly flattened from before backwards. In most instances it lies entirely to one side of the middle line, but occasionally the lower portion may be placed across the mesial plane, and the whole mass then lies obliquely. There are two renal pelves placed one below the other. The ureter from the upper pelvis passes downwards to open into the bladder on the same side, while that from the lower crosses the middle line to open into the opposite angle of the trigone and is naturally much shorter than its fellow. Thus the combined kidney mass usually lies on the side to which the upper portion normally belongs. Papin was only able to find four exceptions to this rule in the 70 cases he collected. It seems that the upper kidney is the "master", and drags the lower across the middle line.

These cases of end-to-end fusion have been split up into smaller groups, to each of which a descriptive name has been given. I feel that this classification is unnecessary, but to avoid ambiguity I shall mention it briefly :—

(1) In the case of the "sigmoid" kidney, the long axis of the combined mass is not vertical, but is inclined from above downwards and inwards, so that a considerable part, if not the whole, of the lower kidney lies on its own side of the body. The ureter draining the upper kidney runs a normal course, while that from the lower pelvis lies entirely on its own side of the body. Thus the ureters do not cross each other, nor

does that from the lower pelvis pass across the middle line. Some authors consider that this form of renal fusion is a connecting link between the horseshoe kidney, and the long kidney. This supposition is untenable if we believe that the horseshoe kidney is due to fusion of similar poles, while the long kidney is the result of fusion of dissimilar poles.

(2) The "long" kidney is similar to the "sigmoid", save that it lies entirely to one side of the middle line. In the great majority of cases it lies on the side normally occupied by the upper kidney. The ureter from the lower pelvis must cross the middle line to reach the opposite angle of the trigone. Formerly this type was divided into two subgroups, according as the ureters crossed each other, or remained uncrossed. This, of course, depends on the relative position of the renal pelves. If the upper is external to the lower the ureters will not cross. If, on the other hand, the upper is internal they must cross each other. When one pelvis lies directly above the other, the ureters may or may not cross.

(3) The L-shaped kidney. In cases of end-to-end fusion, the long axes of the two component parts may not coincide, but may be inclined to each other. When this occurs, one finds that the lower component is always inclined towards the middle line, while the upper is more or less vertical. As a rule, the angle is comparatively small, and the combined mass is shaped like a boomerang. The only effect is that the ureters do not cross each other. On the other hand, if the angle approaches 90 degrees, the fused mass may be described as an "L-shaped" kidney. This term has also been applied to cases where one lateral mass of a horseshoe kidney atrophies, leaving only the isthmus and the opposite lateral mass. These two types of cases have nothing in common, although it may occasionally be difficult to decide to which category a given specimen belongs. If one can make out which pole of the horizontal portion is united to the vertical, one can at once say whether the specimen is an unsymmetrical horseshoe kidney, or a true long kidney.

The appearance of these "long" kidneys is very variable, and only a general description can be given. The combined organs form a sausage-shaped mass, which is usually somewhat flattened from before backwards. The posterior surface is generally smooth, while the anterior is lobulated. The junction of the two kidneys is usually indicated by a distinct notch, but occasionally the fusion is so intimate that the only sign of its occurrence consists in the presence of two renal pelves and ureters. When the line of fusion is visible, one finds that the lower kidney is usually smaller than the upper. The latter lies approximately in its normal position, while the lower kidney may look like an appendage to its inferior extremity.

Usually the renal pelves lie on the anterior aspect of the kidney mass. The next most common arrangement is for both to lie on its inner aspect. In both these groups the lower pelvis lies vertically below the upper, and the ureters may or may not be crossed. In the third group, the upper pelvis lies on the inner side of the kidney mass, while the lower is placed anteriorly. In this group crossing of the ureters is the rule. In a few instances the lower pelvis looks directly backwards.

The vascular supply of the upper portion is fairly constant, and consists of a single normally placed renal artery. That of the lower portion is, on the other hand, markedly irregular, and consists of numerous parallel vessels arising from the lower extremity of the aorta, or from the common or internal iliacs. Usually three or four such vessels are present. Occasionally some of the vessels supplying the lower kidney arise on the opposite side of the body, and cross the middle line to reach the kidney. This arrangement is a clear indication that the lower portion has crossed the mesial plane, and has dragged its vascular supply with it. Except for these crossed vessels, the vascular supply of the lower portion is much the same as that of a simple ectopic kidney.

Embryology.—In cases of fusion of dissimilar poles, I think it most probable that the union took place in a comparatively late stage of ascent of the kidneys. I do not think that it took place during the earliest stage, but that the kidneys did not become fused till they had reached the level of the pelvic brim. The pelvic brim in the fœtus is very different from the pelvic brim after birth. In the embryo there are the two large umbilical arteries, which form a thick lip, on its posterolateral aspects. They narrow the upper orifice of the pelvis, and form an additional obstacle to the ascent of the kidneys. When the upper half of the kidney reaches above the level of the umbilical artery it tends to

fall over it into the iliac fossa. This means that the lower pole rises rapidly upwards, and inwards, and the whole organ lies almost horizontally. It is as if the kidney "took a header" into the iliac fossa. By this means both lower poles are brought close together, while the upper poles are separated by a wide space. It is thought by many writers that fusion of the lower poles takes place at this stage, with the formation of the usual type of horseshoe kidney. My opinion is that the bulk of the evidence favours fusion of the lower poles at a much earlier stage.

Now the two kidneys may not lie at the same level during their ascent. Felix [12] states that it is not uncommon for one to be in advance of the other. When the higher kidney is tumbling over into the iliac fossa, its lower pole may come into contact with the upper pole of the lower organ. It is possible that in this way fusion of dissimilar poles takes place. Now end-to-end fusion is a very rare anomaly, so one would expect that the factors favouring its occurrence would seldom arise. On this hypothesis two conditions must be fulfilled. The first is that the kidneys must not ascend side by side, but that one must be in advance of the other. The second is that when the upper kidney is passing the brim of the pelvis, its lower pole must come in contact with the upper of the opposite organ. It is unlikely that both these conditions would be satisfied at the same time. In addition, the root of the mesentery lies between the two organs, and would tend to prevent contact from being often made.

Once fusion has taken place, the upper kidney continues its ascent, and drags the lower after it. It may drag the lower completely across the mesial plane, with the formation of a "long" kidney, or the lower may remain partially on its own side of the body, thus forming a "sigmoid" kidney. Formation of an L-shaped kidney takes place when the ascent of the combined mass ceases before the lower portion is pulled into line with the upper.

One of the chief reasons why I believe that in this condition fusion takes place at, or near, the level of the pelvic brim, is that the lower portion is occasionally supplied by vessels arising from its own side. This means that it must have formed contact with these vessels before it became fused with its fellow organ, or at least before it was dragged across the middle line. Now these vessels correspond with those usually found supplying a simple ectopic kidney placed at the brim of the true pelvis. Therefore, fusion probably occurred when the lower kidney lay somewhere near the brim of the pelvis. In most instances it seems that the lower organ must have broken its vascular connexions with its own side of the body, and acquired fresh ones on the opposite side. There is no reason why this should not happen, as there is a series of segmental arteries supplying the mesonephros on each side of the body, and the kidney can draw its blood supply from those in its immediate vicinity.

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THE PRESIDENT: Mr. Swift Joly has dealt fully with problems in the pathology and embryology of his subject. As surgeons we recognize many developmental abnormalities, especially examples of the horseshoe kidney. In the last eighteen months I have removed stones from four such cases. Pyelolithotomy presents no difficulty; the anteriorly placed dilated pelvis is as easy to approach as in a normal case, but where stones in calyces can only be removed by incision of the parenchyma a difficult situation arises from the anchor-

age of the isthmus and the irregularity of the main renal vessels. Vascular control is hazardous and manipulation of the kidney for removal of the stones uncertain. These difficulties may be largely overcome if the isthmus be divided (symphysiotomy), a procedure practically immune from the risk of hæmorrhage if interlocking mattress sutures are placed on either side of the line through which the incision, effected with the high-frequency knife, is made. Thus freed, the vessels, though irregular, may be seen and easily controlled, and the kidney explored at will. Further supplementary fixation of the kidney at a higher level and more superficially, straightens the ureter, thereby aiding renal drainage, and placing the kidney in a more accessible position, should subsequent operation upon it ever be required. Symphysiotomy may also relieve the pain of pressure upon pre-vertebral sympathetic nerves, as was pointed out to this Section many years ago by Frank Kidd, and also by Mr. Clifford Morson at this meeting.

Section of Radiology

President—PETER KERLEY, M.D.

[*March* 15, 1940]

JOINT MEETING WITH THE BRITISH INSTITUTE OF RADIOLOGY AND THE FACULTY OF RADIOLOGISTS

X-ray Diagnosis in Chronic Arthritis

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To obtain an accurate diagnosis in cases of chronic arthritis four essential points must be observed: (*a*) Morbid history, (*b*) clinical examination, (*c*) laboratory findings, and (*d*) X-ray pictures.

The diagnostic value of X-rays in chronic arthritis is shown by (1) early detection of arthritis, (2) diagnosis of the form of arthritis, (3) appreciation of anatomical changes.

(1) *Early detection of arthritis.*—The value of X-rays in the early stages of chronic arthritis is shown mostly in cases involving deep-seated joints, e.g. the spine and hip-joints, which are not easily accessible to direct clinical examination. X-rays are specially valuable in cases of degenerative arthritis (osteo-arthritis or arthrosis),[2] where the early symptoms are so slight and so confusing that the clinical examination gives us nothing definite. Here the value of X-ray examination is pre-eminent. At present whenever osteo-arthritis in the hip-joint is suspected, the X-ray changes are generally quite typical, although the clinical picture may be still doubtful; but owing to improved methods of investigation of this condition this statement may have to be modified in the near future.

(2) *Diagnosis of the form of arthritis.*—The division of chronic arthritis into two main groups, atrophic or inflammatory arthritis, and hypertrophic or degenerative arthritis, is becoming more generally accepted. In arriving at this classification the X-ray findings are of definite value.

(3) *Appreciation of the anatomical changes.*—Even when the X-ray film fails to differentiate the form of arthritis or when the diagnosis is already ascertained by other means, X-ray examinations of the affected joints will be of help:—

(*a*) In the development of the disease, it is important to appreciate the amount of damage caused to the different joint-structures, such as erosion, eburnation, and displacement of the joint surfaces. Radiography is of the greatest importance for the management of these cases, especially in connexion with preventive or curative orthopædic measures.

(*b*) When the disease has become quiescent, X-ray examination may be the only way in many cases of determining the amount of damage. While arthrosis is a slowly evolving disease which never presents signs of true repair, in atrophic arthritis, even in aged persons, radiographic evidence of anatomical repair may be seen corresponding to remarkable clinical improvement.

[1] This paper was read at the meeting by Dr. Forestier.

[2] In this paper the term arthritis is used for rheumatoid and infective arthritis, and the term arthrosis for osteo-arthritis.

Difficulties and Limitations of X-ray Diagnosis in Arthritis

(*a*) Under present technical conditions X-ray changes in the joints do not appear very early in certain groups. This is especially true of acute or subacute arthritis. For the first few weeks, a very marked arthritis with outstanding clinical features may give no radiographic signs. In some chronic cases, in which pain, swelling and limitation of movements have existed for some time, the X-ray picture may be normal, and the first signs of bone atrophy may not appear until a few months have elapsed.

(*b*) In many cases the precise cause of the arthritis is not apparent from the X-ray examination. Taylor and his associates have rightly stated that the appearance of a gonococcal arthritis of six weeks' duration may closely resemble that of the tuberculous joint of six months' duration. No interpretation as to the cause of arthritis can be made if the radiologist is not told of the duration and the severity of the joint symptoms.

(*c*) In the later stages of any case of chronic arthritis, whatever its form, and perhaps in the course of every case of chronic disease of the joints, there is a natural tendency to the development of osteo-arthritic (arthrosic) changes. These degenerative changes appear not only in true osteo-arthritis, but also, when the patient reaches a certain age, as a consequence of trophic changes, abnormal static conditions or strain, or even after bone disease such as osteitis fibrosa. In middle age, or later, there is a normal senile decalcification of the whole skeleton, so that when assessing decalcification in a given area, comparison should be made with the homologous bone and joint structure and not in terms of pure photographic appearance.

(*d*) For these reasons, in cases of long-standing arthritis, especially in aged patients, atrophic and hypertrophic changes are so completely superimposed on the same joint that the X-ray picture is of very little value in determining the primary nature and form of the disease.

Conditions Required for Correct Radiographic Interpretation of Arthritis

(*a*) The teaching of the anatomy of the bones and joints with the help of radiography is most important for those who intend to specialize in radiology, orthopædics and rheumatology. Such teaching has been started in England in some medical schools. No one can judge of the radiological changes in a joint or in a bone if he is not familiar with the normal shadows cast by these structures.

(*b*) Equally desirable, but much more difficult to achieve, is a sound knowledge of the pathology of joint conditions. In a few museums, such as the Strangeways Collection at the Royal College of Surgeons, specimens of joints are available for such a study, but they are mostly long-standing cases where the typical features of the disease may be confused with more remote secondary changes. There remains the possibility of watching those pathological changes in three different ways: during a surgical operation, at post-mortem examination—a very rare opportunity, and in dry bones. Though these dry specimens are imperfect in that they show only part of the joints, they are of great value to the radiologist, since in them may be studied almost the only part of the joint accessible to X-ray examination.

Whatever may be the value of X-ray diagnosis in chronic arthritis, the interpretation of the films should describe the anatomical changes accurately and *only suggest* the possible diagnosis.

In many cases, numerous films are desirable, but, for economic reasons, are not always obtainable. The value of the standard film of the hand advised by Gilbert Scott is well established and it was adopted by Louis Duvernay as far back as the year 1926.

It is often helpful to take a film of the joint on the opposite side in order to check structural or postural abnormalities. When dealing with the spine, one film, whatever the region, is of little value unless checked by at least one other film taken in a different plane. The recent development of the examination of the interneural joints by oblique views of the lumbar spine shows that it is still possible to improve our investigations by new techniques.

A good following-up by repeated X-ray examination is a necessity in the management of chronic arthritis, both for treatment and prognosis.

Sometimes it is advisable to radiograph parts of the body distant from the affected region. For example, if X-ray changes suggestive of Paget's disease are visible on a

joint film, the skull should be examined. Again, if a young patient is referred with a history of repeated low back pains and the radiogram fails to reveal any abnormal changes in the spine, Gilbert Scott advises an X-ray film of the sacro-iliac regions to determine the presence of ankylosing spondylarthritis in the pre-ankylosing stage.

Interpretation.—When interpreting a radiogram of an arthritic joint the following points should be noted: bones, joint space, capsule, ligaments, soft tissues and posture.

(*a*) The bones should be carefully examined as regards shape, which may remain unaltered in the articular region, or become dentate or even eroded by a superficial or deep ulceration. Conversely, bone production frequently occurs on the border of the articular surfaces. The calcification of the bones is the second point of importance, and is usually greatly disturbed in any form of arthritis. Local, regional, and general decalcification have a different meaning. The latter appears in old age and in a few generalized conditions. Gilbert Scott has pointed out the importance of the disturbance of the bone density balance between the cortex, the medulla and the cancellous bone of the epiphysis. In degenerative arthritis, hypercalcification and bony sclerosis are some of the main features. The trabeculation in the epiphysis may be greatly altered. It almost disappears in the course of inflammatory arthritis, and becomes rough and uneven later on, in the stage of repair.

(*b*) The joint space is usually diminished in width, either entirely or in part, and may become cloudy or actually disappear.

(*c*) The soft tissues: Synovial lining, capsule, ligaments and tendons are not easily detected except in films taken with low penetration. Taylor and his co-workers stress the great importance of soft tissue radiograms in the study of arthritis.

(*d*) The posture, especially of the weight-bearing joints, may be disturbed in arthritis from deformity of the joint surfaces, lateral displacement and subluxation of the joint, and muscular spasm. An exact knowledge of these postural changes is of great importance to the orthopædic surgeon.

Arthritis and Arthrosis

True arthritis or arthritis in the sense of an inflammatory disease of the joints, is generally caused by infection, but can be originated by any other stimulus such as allergy, metabolic disturbances, neurovascular changes, &c. The common link between all these forms is that, clinically and pathologically, they show the typical features of inflammation: vasodilatation, swelling, and increase in local temperature, followed by bone calcium absorption.

The term arthrosis is applied to all degenerative processes whatever their cause may be. They are more torpid and occur in the second part of life. The term arthrosis seems better suited to the conditions than the word osteo-arthritis, used in the English-speaking countries, because the terminal "itis" is given to inflammatory conditions and the terminal "osis" to degenerative conditions.

Arthrosis (osteo-arthritis) is more frequent in the weight-bearing joints. The first changes appear in the articular cartilage, in the form of a fibrillation of its substance, which becomes worn by constant trauma. It tends to the gradual erosion of the cartilage and densification of the underlying bone (eburnation). The synovial lining is either moderately affected or not at all, but at the edges of the articular surfaces there is a tendency to new bone growth, and spur formation (osteophytes). Occasionally special forms of decalcification may be observed: decalcification in patches, or malacic deformation. In any case, there is no tendency to ankylosis, and the evolution is slow.

True arthritis or inflammatory arthritis (infective and rheumatoid) may appear in youth as well as in old age. It is a much more extensive disease and is sometimes systemic. The pathological changes start in the synovial membrane, first by swelling, then by permanent thickening from inflammatory infiltration (proliferation of Nichols and Richardson). This process tends to the development of synovial fringes inside the articular cavity, which may join in a wide pannus. This inserts itself between the articular cartilages, adheres to them and lastly erodes them. The final stage is the destruction of the joint cavity, exposure of both epiphyseal ends, erosion of the bone and ankylosis. It is often associated with lateral deviation and bone displacement. Histologically, the synovial membrane and its pannus have the texture of a granuloma, with infiltration of round cells and, later on, of conjunctival and fibrous cells, which

may be the cause of fibrous adhesions. But, contrary to what happens in arthrosis, this pathological process may become arrested and sometimes stabilization and repair can be observed; this never happens in arthrosis.

Some malacic changes may also occur in torpid forms of inflammatory arthritis, but one of its typical consequences is the ossification of the peri-articular ligaments, causing bridging between the adjoining bones (syndesmophytes), a process which is entirely distinct from the bone formation in arthrosis. The latter does not tend to ankylosis.

Radiological Signs of Inflammatory Arthritis

These may be divided into three stages: at the onset, in the course of development, and at the terminal stage of arthritis.

(1) *Onset.*—In chronic inflammatory arthritis of mild degree, the X-ray picture of the affected joints may be entirely negative for a period of several weeks to two or three

Fig. 1.—Infective arthritis of the knee-joint. A typical picture of local bone erosion in a femoral condyle—general bone decalcification.

months. The essential sign is bony decalcification. This appears locally, and is specially marked on the epiphyses of the affected joints. The cancellous bone becomes still more transparent than the cortex or the medulla. The decalcification may also be regional, affecting wide areas, for example in the carpal or the tarsal bones when clinical signs are observed only in the interphalangeal or metacarpo- and metatarso-phalangeal joints. Later on the decalcification becomes general in the rheumatoid form, which is truly a systemic disease with loss of weight, anæmia, mild temperature, &c. In old patients, who show a normal osteoporosis, the interpretation of these early changes is more difficult.

(2) *Development.*—The decalcification by now has increased and presents several forms. Sometimes both epiphyses are uniformly decalcified and it is impossible to get well-contrasted films. More often there is a mottled appearance with innumerable spots of decalcification which are not quite confluent. When the decalcification is advanced in the subchondral zone, it may lead to an irregularity of the outline of the bone, and in

subsequent films, to a small loss of substance, which is a picture of an ulceration of the cartilage with bone exposure. Such a picture is absolutely typical of infective conditions and is never seen in arthrosis (fig. 1). Very often (mostly in the hip and in the wrist) in the absence of such erosion, the loss of calcium is so marked that the contours of both epiphyses disappear and it is impossible to recognize any joint space (fig. 2). Such a picture does not necessarily mean complete loss of the cartilage, since we have seen cases where there has been partial reconstruction. In such cases, the joint space disappears on the film not only by gradual thinning all over the surface, but also by loss of transparency of the space itself which becomes more opaque and cloudy through inflammatory deposits (fig. 3).

FIG. 2.—Inflammatory arthritis (rheumatoid) of the hands of several years' duration. The changes in the interphalangeal joints are not typical; local osteophytic formations on the proximal interphalangeal joint of the ring finger. The inflammatory nature of the changes is proved by the general decalcification of the bones and the marked changes in the carpus.

Examination of the soft tissues may reveal the thickening of the synovial membrane and sometimes synovial effusion.

The postural changes, especially in the deeper joints, may be detected radiographically even when they are not clinically apparent, e.g. subluxation of the head of the femur,

posterior dislocation of the head of the tibia, lateral deviation of the metacarpals and phalanges. In other cases, where the clinical deformation is more apparent, radiograms may show more accurately whether the postural changes are caused by subluxation, bone destruction or by muscular spasm.

(3) *Stabilization and repair.*—Unlike the arthrosic forms, inflammatory arthritis may come to stabilization and even repair, when the causative agent has lost its activity.

If the damage has been extensive, the final deformity will remain. Recalcification will take place: partial, irregular, with some sclerotic patches here and there. The contours

FIG. 3.—Inflammatory arthritis (rheumatoid) of the hip-joint. Bone erosion on the upper part of the acetabulum—bone contours cloudy—joint space almost disappeared—slight arthrosic reaction on the acetabulum.

ot the epiphyseal bone will appear more clearly, but there will be no reconstruction of joint space or recovery of movement lost through fibrous or bony ankylosis.

If the causative agent is eliminated at an early stage, not only will recalcification take place with a more clear-cut outline of the bones, but a partial restoration of the joint spaces may be observed. The latter becomes more defined, less cloudy, and the regular use

of the joint which has become painless may restore its movement more or less perfectly. The restored joint space will be narrower than previously, just as the bone density will not be as perfect as before. These anatomical changes indicate repair and they will be accompanied by partial restoration of function. They may sometimes be associated with most interesting arthrosic features in the form of osteosclerotic areas in the sites of pressure, and formation of small and irregular spurs at the edge of or at some distance from the articular surfaces. This reactive arthrosis can be differentiated from true arthrosis by the moderate amount of bone formation, the irregularity of the bone calcification, by the dentate form of the joint space when it is visible, and still more typically by the persistence of a small area of ulceration, which never heals completely. None of these is to be seen in true arthrosis. These secondary changes are generally symptom-free.

FIG. 4.—Arthrosis (osteo-arthritis) of the knee-joint. Typical picture of the early changes—increased calcification, osteophytic formation on the inner part of the joint space and on the spinous processes. The joint space itself is only slightly diminished.

Radiological Signs of Arthrosis (Osteo-arthritis)

Here the changes are not in definite periods since the evolution of arthrosis is much more torpid and continuous, and usually goes on progressively without repair. The radiological changes in the different parts of the joints are as follows:—

(*a*) *Calcification.*—The first change in an arthrosic bone is a change in calcification, which, in the great majority of cases, is a local hypercalcification. When assessing these

changes, we must take into account the normal loss of bone density in old persons where arthrosis exists and compare the suspected joint with the opposite one which is supposedly healthy.

Hypercalcification appears in the subchondral area of the epiphysis, especially in the weight-bearing area. It tends gradually to develop over the whole surface and also towards the centre of the epiphysis. Usually this change appears in both bones forming the joint. Hypercalcification does not mean hard bone, but, on the contrary, the increase of calcium

FIG. 5.—Arthrosis (osteo-arthritis) of the cervical vertebræ, lateral view. The three upper vertebræ are normal. C. 4 to C. 7 show bone sclerosis, coarse trabeculation, "shrinking" of the vertebral bodies, osteophytic formations on the angles of the vertebræ and thinning of the intervertebral discs, which have become less transparent. The articulations of the facets are practically normal.

goes with the progressive loss of the trabeculation of the epiphysis which brings about the softening of the bone substance, and, later on, plastic changes in the contours of the epiphysis; flattening of the bony ends, and marginal lipping (fig. 4).

Less commonly, local decalcification may occur in the course of arthrosis. This is especially to be seen in the hip-joint. It appears in the form of rather large patches of

decalcified bone, sometimes circular, sometimes polycyclic in the centre of the head of the femur and, more rarely, in the roof of the acetabulum. It must be pointed out that even when they are superficial, in the subchondral region, they never destroy the cortex; the contours of the epiphyseal ends never become irregular, as is the case in infective arthritis. These patches do not show any wall for many months or years; but, later on, a thin layer of condensed bone may give them the appearance of a cyst. It is doubtful whether they can disappear entirely in the course of the disease. They are probably due to local obliteration of bone arteries, promoting local aseptic necrosis. When examined at operation, they appear as small cavities with no differentiated wall and full of amorphous matter composed of degenerated fat and small crystals (Huc and Benoit).

FIG. 6.—Arthrosis (osteo-arthritis) of the fingers. The distal interphalangeal joints of the first three fingers are irregular and distorted. The changes are not typical and could develop as well from an old-standing infective arthritis as from osteo-arthritis. The absence of any pathological change in the carpus rules out the first suggestion.

From our experience, and contrary to Gilbert Scott's opinion, these decalcified patches may appear early in certain forms of hip-joint arthrosis. They may precede the changes in the joint space and are not associated with active formation of new bone. They represent a distinct form of hip-joint arthrosis and a painful one; night pains are generally

intense, as if the contents of the decalcified areas were acting as an irritating foreign body.

Sometimes decalcification may exist far from the joint itself, in the shaft of the bones. These areas are much less defined and there is no change in the trabeculæ. They are in contrast with the general calcification of arthrosic bones which are generally more calcified than the rest of the body.

(*b*) *Trabeculation.*—Except in the subchondral zone, gross changes in the trabeculæ do not appear at an early stage. In the cortex they disappear and are replaced by the uniform dense shadow of opaque bone (osteosclerosis). At a distance from the joint space, the

FIG. 7.—Arthrosis (osteo-arthritis) of the hip-joint of several years' duration. Bone densification and bone sclerosis on the weight-bearing part of the joint; the joint space has almost disappeared in the same area. Flattening of the head of the femur; osteophyte formation on the acetabulum; slight tendency to external subluxation.

trabeculæ of the bone become thicker and rougher, but their strength is not increased, since some deformation of the bone may occur where pressure is exerted. In the short bones of the wrist and in the cervical vertebræ there may occur some shrinking, with a coarser trabeculation (fig. 5).

(*c*) *Bone contours.*—The osteosclerotic bone can undergo plastic changes in its contours. We have quoted the flattening of the head of the femur and the marginal lipping of the

horizontal faces of the vertebræ. The contours of the bone may be altered by new bone formation. Most of it appears at the edge of the cartilage, in the form of spurs. They are the osteophytes which will be described in a special chapter, but the bone formation may also take place in the joint space itself. Such are the superadded bone layers inside the acetabulum which tend to expel the head of the femur out of the cavity.

(*d*) *Joint space.*—The gradual thinning of the joint space in arthrosis is one of the essential characteristics of the disease. It appears, in most cases, before new bone formation, or marked changes in the calcification. At first it never involves the entire joint space, and it is associated with marked hypercalcification of the adjoining bones instead of decalcification. These changes in the joint space are quite different from those of inflammatory arthritis. They may appear in three different instances :—

In non-weight-bearing joints such as the interphalangeal joints, the joint space appears a little irregular and loses a part of its width, but more on one side than on the other, taking a wedge shape (fig. 6).

In a joint with a large articular surface, such as the knee, the thinning of the joint space occurs on one condyle only at the beginning, thus causing a change in the joint posture.

In a joint with a small articular surface, such as the hip-joint, the thinning starts on the weight-bearing segment and extends laterally and medially until all the upper part of the joint space has disappeared (fig. 7).

In rare cases, for no explained reasons, the narrowing of the joint space starts in its inferior portion near the sulcus of the acetabulum.

In every case, the joint space disappears slowly and progressively. It remains regular and never shows punched-out areas as in gout or infective arthritis.

When bone formation is active, osteophytes, or chondrophytes may become loose in the joint cavity where their shadows appear. More rarely, these varied bodies are due to detached parts of the fibro-cartilage.

(*e*) *Soft tissues.*—These rarely show outstanding features in arthrosis. In a few cases, the capsule of the joint may be slightly infiltrated with calcium and cast diffused shadows. The tendons or the ligaments may show, when calcified, small spurs at the point of their attachment to the bones. They differ from the osteophytes in that they appear further from the joint space. Calcification in the peri-articular bursæ may cast irregular shadows. Sometimes calcified glands or arteries may be seen near the arthrosic joint. All these changes are of little significance.

(*f*) *Postural changes.*—In arthrosis postural changes may occur through the wearing out of the articular bones, which become softer. In the knee, these will cause pathological genu-valgum or varum, and in the spine wedge-shaped vertebræ. But these changes may be the result of new bone formation, such as external subluxation of the femoral head by bone apposition in the acetabulum. Greater postural changes may still appear if some regional malacia takes place and when the joint loses entirely its normal shape—(*tête coulée*).

Radiological Syndromes

(1) Osteophytes ; (2) syndesmophytes ; (3) malacia.

It is worth while describing separately three groups of structural changes which occur in the course of chronic arthritis.

Five years ago we called attention to the distinction between two sorts of bone production, which are entirely different in their appearance, character and consequences.

(1) *Osteophytes.*—These are bone outgrowths which arise from a large base on the edge of the epiphyseal bone and tend to develop into spurs directed obliquely towards the joint space. On the vertebræ these spurs are not implanted on the edge of the body but at a small distance on the lateral aspects. The thickness at the base, the existence of a cortex on the surface, and the fact that their centre is made of cancellous bone, which, though abnormal, is in continuation with that of the articular end, are characteristic. When they develop on both edges of an intervertebral space, they grow towards one another, and may come in contact, but have no tendency to join each other. For these reasons, ankylosis does not occur, and the limitation of movement caused by the osteophytes is very small and due purely to the volume of the bone formations which tend to increase the width of the articular surfaces.

(2) *Syndesmophytes.*—The bone formations which we call syndesmophytes and are described in English-speaking countries as "bridging" are quite different and usually much thinner than the osteophytes. At the beginning they appear on an intervertebral

space, where they are most characteristic, as faint shadows with ill-defined borders. Later on they are seen as opaque lines, slightly curved, uniting one vertebra to another. They have no cortex. When they become thicker, they consist of dense bone, formed by ossification of the intervertebral ligaments. From the very outset and even before they can be accurately detected on the radiograms, they tend to stiffen the joint, and very often fibrous ankylosis precedes bony ankylosis. In contradistinction to the osteophytes which impair joint movements very little and only then through their excessive development, the syndesmophytes are early ankylosing agents. Syndesmophytes which are typical

FIG. 8.—Advanced inflammatory arthritis of the cervical vertebræ (ankylosing spondylarthritis). The cervical vertebræ are one rigid mass through ossification of the anterior longitudinal ligament. Normal height of the intervertebral discs which appear less transparent.

of ankylosing spondylarthritis are always associated with complete ankylosis of the affected segments of the spine (fig. 8). This ankylosis is due, not only to the bridging of the vertebral bodies, but also to the bony union which takes place simultaneously in the small articulations of the facets with ossification of the ligamenta flava. This is the reason why it is so important that the radiologist should discriminate, at the earliest possible period, between the osteophytes which belong to the common vertebral arthrosis

(spondylarthrosis = spondylitis deformans) which impair the movements of the spine but little, and the syndesmophytes, which, even when they can be detected only on a few intervertebral joints will tend, later on, to develop into the typical poker spine. With Coliez in 1936, we have studied a remarkable dry specimen of ankylosing spondylarthritis, and we have proved that even when large bands of ossified ligaments were uniting the vertebræ and bringing on full ankylosis, the X-ray pictures showed but a few syndesmophytes. The reason is that these ossifications, being made of thin layers of calcium, cast no opaque shadow when they are struck normally by X-rays, and their presence is detected only when they are struck by tangential rays, thus producing the typical shadow of " bridging ".

FIG. 9.—Local malacia as the result of an infective arthritis in the hip-joint. The trophic changes have been limited to the deep part of the acetabulum and have resulted in the typical picture of protrusio acetabuli. The changes in the joint space are suggestive of a secondary arthrosis in a previously rheumatoid joint.

The syndesmophytes are seen most frequently in the spine, and they are almost always preceded by radiological changes in the sacro-iliac joints (as described by Gilbert Scott, Buckley, &c.). We have shown (Forestier, 1939) that these radiological changes in the sacro-iliac joints appear when the spine itself looks normal. The typical points in the radiographic picture of sacro-iliac joints in the pre-ankylosing period of spondylarthritis

are: (1) The pseudo-widening of the sacro-iliac joint space, caused by the decalcification taking place in the subchondral part of the sacrum and ilium. (2) Later on, it develops in a wide area extended far from the joint space. (3) It is only in the last stages that the sacro-iliac ligaments become ossified and tend to obliterate the entire joint space. This obliteration is due to a syndesmophytic process. This year, we have described with our pupil, Vuillermet, (Thèse Lyon, 1940) a new clinical entity where syndesmophytes appear not only in the spine, but on the joints of the limbs. This syndrome, which we

FIG. 10.

FIGS. 10 and 11.—Local malacia in the course of arthrosis (osteo-arthritis) of the hip-joint. The pictures have been taken with an interval of three years. In this case the lesion has developed on the head of the femur which has become softer and has been deformed as the result of the pressure (*see* p. 29).

have labelled *panarthrite engainante*, tends to bring about a complete ankylosis of practically all the joints of the body, the patient becoming entirely rigid. The radiograms of the hip-joints, the knees, and the carpuses of those patients show a ligamentous ossification in long parallel streaks, which unite the bones of each joint. This condition, like ankylosing spondylarthritis, affects youngish patients.

Significance of osteophytes.—It is generally accepted nowadays that the mere presence of scattered osteophytes on the lumbar vertebræ of middle-aged or old patients has practically no pathological significance. Osteophytes are one of the typical elements

of arthrosis only when they are associated with the other radiographic characteristics of the syndrome.

There are osteophytes which we do not consider truly pathological and which we have labelled reactive osteophytes. They appear after the age of 40 on the articular segments subjected to strains or abnormal postural conditions. The strain may be occupational (e.g. labourers and workmen) or due to some congenital abnormality (scoliosis). These osteophytes are a mode of adaptation to the new conditions and are symptom-free. We have already described the small and irregular osteophytes which may appear at the terminal stage of true arthritis in its infective or non-infective forms. Like the latter, they cause no symptoms; they also belong to the class of reactive osteophytes.

FIG. 11.—Same case as fig. 10, three years later.

The osteophytes which appear in association with the other typical arthrosic changes are quite different. They generally develop at a later period, after thinning of the joint space and hypercalcification of the epiphysis. In some cases their growth is very extensive and they occur most frequently in the hip-joint and in the knee. An increased bone formation on the edge of the acetabulum and around the head of the femur may cause a certain amount of restriction in the movements due to the volume of the new-formed bone. But still more, these exuberant osteophytes may be responsible for severe pains which are largely due to mechanical compression of the adjoining tissues and to spells of local congestion as a result of minimal traumas, or minute fractures due to some abnormal movements.

(3) *Malacic deformity in arthritis and arthrosis.*—This is not a very common event in the evolution of chronic arthritis. It appears under different conditions and is characterized by the gradual softening of a part of the articular area. This is different from osteoporosis which is much more widely distributed, and does not affect the trabeculation. The second distinctive character is, that in osteoporosis, the outline of the bones is unchanged or only slightly affected, while, in malacia, the shape of the articular ends may be absolutely remodelled.

Among these typical malacic changes, we can describe two kinds in the hip-joint. When the upper part of the acetabulum is affected, it may take an oval instead of spheroid form, but generally, when malacia is limited to the centre of the acetabulum, the head of the femur tends to protrude into the pelvis (fig. 9). This is the typical protrusio-acetabuli which can be congenital but may be observed in the terminal period of arthritis. The second sort of malacic change to be seen in the hip-joint is the "melted head" (*tête coulée*), when the head of the femur becomes soft, and through static pressure becomes flattened at its upper part, while the lower part becomes more developed and takes an abnormal shape (figs. 10 and 11). This condition is to be seen in the course of arthrosis and leads to great impairment of the movements of the joint.

Malacia may be also observed as a result of strain in workmen subjected to hard work, and we have seen a case affecting the ulna.

Special X-ray Syndromes in Various Joints

Finally, there are the X-ray appearances which are to be seen only in certain joints.

Spine.—In addition to the common types of degenerative spondylarthrosis (spondylitis deformans) and inflammatory (ankylosing spondylarthritis), there are certainly a number of cases which cannot be put either in one group or the other. Among the latter, there is what we should call the "third rheumatic disease of the spine" consisting of bone growth alongside the dorsal segment of the spine, and occurring mostly in old persons and more frequently in men than in women. These patients are heavily built and have a slight dorsal kyphosis. It tends to the partial limitation of movements of this segment with little impairment in the movements of the ribs (as against the condition occurring in ankylosing spondylarthritis).

Radiologically, the disease starts in the forepart of the vertebral bodies and of the intervertebral discs. The edges of the body become condensed but more malleable, and come in contact across the diseased peripheral part of the disc. They are neither true osteophytes nor syndesmophytes. Typically, the radiological changes in this disease are those of bone growth in the form of a thick layer of cancellous bone uniting only the forepart of the bodies. In dry bones this bone growth has the form of a succession of "pads" corresponding to the intervertebral spaces, as if the newly formed one was softened and shrunk by pressure. In this disease, contrary to spondylarthritis, the facet joints are free from ankylosis, but a Norwegian radiologist, Bakke, has called attention to the ossification of the insertions of the ligamenta flava, a condition which one of us described nineteen years ago as a possible cause for certain forms of old-age kyphosis.

Another vertebral disease which is commonly misinterpreted and is still more frequent, is what we called in 1936: *arthrose ménisco-somatique*. It differs from the other forms of vertebral arthritis or arthrosis, which are more or less generalized or systemic diseases, in that it is a focal disease involving one intervertebral joint and affecting essentially the intervertebral disc and the opposing faces of the upper and lower vertebræ. It begins with the narrowing of the intervertebral space associated with the slight densification of the bony lamellæ of the adjoining vertebral bodies. In two or three years, the disc has almost disappeared and the vertebræ exhibit an increased bone density on the opposing faces; in lateral views, the bone edges curl against one another in a typical lipping (fig. 12). Lipping is different from osteophytes in that it is not a growth but a deformation, that it is situated exactly in the angle of the body and that it is associated by true sclerosis in the "bony lip" and the adjoining area.

We have observed over 100 cases of this condition which is essentially different from common arthrosis in the spine, not only because it is strictly limited to one or two joints, but also because it attacks youngish persons, especially tall, thin and slender women, and predominates in the lumbar region and mostly in the lumbosacral joint. In the begin-

ning it is often mistaken for tuberculous spondylitis, but it never causes erosion of the vertebræ and tends to bone densification without bone atrophy or destruction. We have been able to follow up one case for eighteen years and in no instance has there been any symptom of cord compression. The nature of the condition is unknown. Possibly certain cases are traumatic, sometimes a latent infection is probable; in many others no definite origin can be detected.

FIG. 12.—" Menisco-somatic arthrosis "; lateral view of the lumbar vertebræ. An unusual radiological picture, quite distinct from the common spondylitis deformans (osteo-arthritis). This is a focal lesion involving one intervertebral joint only. Progressive thinning of the discs; osteosclerosis of the adjoining vertebræ; lipping of the same vertebræ; a chronic condition. No abscess formation.

Differential diagnosis.—X-ray examination is of definite value in the differential diagnosis of chronic arthritis. Many patients who are referred to the radiologist for more or less defined symptoms in their locomotor system, and are labelled rheumatism or arthritis, are affected with a bone disease which can be detected only by X-rays, when they are limited to deep-seated bones: e.g. Paget's disease, Recklinghausen's disease (osteitis deformans and osteitis fibrosa). We have met with a number of cases of so-called hip-joint arthritis which the X-ray films revealed as being due to some Pagetic condition in the pelvis and the femur. This bone condition is often limited to this area and is worth a special description, which we have in preparation.

Some abnormalities in the bones and joints may be detected radiographically while the clinical picture is leading to the diagnosis of arthritis. Among these are congenital subluxation of the femur (coxa plana) in the hip-joint; and cuneiform vertebræ, spondylolysis, and spondylolisthesis in the spine.

The differential diagnosis between chronic arthritis and the specific forms of pyogenic and destructive arthritis is certainly helped by X-rays. In the latter conditions the importance of bone destruction is far greater than in non-specific arthritis.

The help of X-ray examination in the diagnosis of gout is moderate. In the early

stages, there are few joint changes to be seen, and at a later stage, when localized areas of atrophic destruction of bone are present on the shaft and ends of the small bones of the hand or the foot, some tophi can be detected by palpation. In fact, "punched-out areas" eroding the cortex, *halberds* of the French, are typical pictures of gout, but they are not early radiological signs. Unfortunately, the so-called typical transparent spots on which the diagnosis of gout is often based, do not belong to this disease only and we have observed a number of similar patches in the phalanges and the metacarpals in the course of undoubted cases of rheumatoid arthritis.

M-P. Weil and Destrez have claimed that gout and arthrosis were very similar diseases since they were both able to form osteophytes. We have attempted to prove in the course of this report that these formations are not pathognomonic and have no pathological importance in patients past middle age. We have seen osteophytic formations in the vertebræ of typical cases of Paget's disease, and there is no similarity between the latter and arthrosis.

One of the most difficult problems which may confront the radiologist is the determination of the value of a traumatic factor, in the cases of so-called post-traumatic arthritis. The answer is sometimes impossible. Many difficulties would be avoided in compensation cases if a radiogram was taken immediately after the accident, if the patient is of the "rheumatic age."

Suggestions for Improvement in X-ray Diagnosis

However important have been the results arrived at from X-ray diagnosis of arthritis in the last two decades, there remains much more to be achieved.

(*a*) Study of positioning for each joint, in order to afford a better comparison between films taken at different periods.

(*b*) Comparative gauge for decalcification.

(*c*) A more thorough exploration of the upper dorsal segment of the vertebræ and of the lumbosacral joints.

(*d*) Improvement in the knowledge of the conditions of the soft tissues.

We have not mentioned the combined method of injections of opaque or transparent fluids into the joint cavities, since they have not yet produced any definite advantage, in spite of the valuable contribution of Bucher and Oberholzer.

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Section of Psychiatry

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Simultaneous Respiratory and Electro-encephalographic Recordings in Cases of *Petit Mal*.—W. SARGANT, M.R.C.P.

[Abstract of paper read at April 9, 1940, meeting.]

Voluntary hyperventilation is often used as a diagnostic procedure to produce seizures in cases of *petit mal*. This investigation was to find out if alterations in breathing ever occurred spontaneously under experimental conditions, and if so whether this was in any way related to the incidence of attacks. Synchronized respiratory and electro-encephalographic recordings were therefore made on six cases of *petit mal* having frequent seizures throughout the day. In these cases 46 respiratory recordings were made, either on a basal metabolic rate machine or an air spirometer synchronized with the electro-encephalograph.

Some of the results obtained were shown in a series of slides.

In three of the cases a correlation was present between spontaneous increase in the minute respiratory volume and increase in the incidence of abnormal waves in the electro-encephalograph. A similar correlation was present in these cases when respiratory changes were induced rather than allowed to occur spontaneously. Overbreathing of carbon dioxide abolished the abnormal brain waves in these cases. In three other cases no correlation was demonstrated. These results suggested that in cases of *petit mal* particularly susceptible to the effects of a gaseous alkalosis, small spontaneous alterations in breathing may sometimes alter the incidence or duration of fits. Breathing changes are known to occur in some subjects with emotional upset; it is possible that emotional hyperventilation is one of the means by which *petit mal* attacks may be increased in states of anxiety.

This work was carried out in conjunction with Dr. Robert S. Schwab and under the supervision of Dr. Stanley Cobb at the Department of Psychiatry, Massachusetts General Hospital, Boston, U.S.A., and reported more fully in *Arch. Neurol. Psych.*, Chicago, 1939, **42**, 1189.

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Observation Units

By E. N. BUTLER, M.R.C.S., L.R.C.P.

THE observation unit at St. Francis' Hospital and the type of work which is done there has been admirably described in a paper by Pentreath and Dax in the *Journal of Mental Science* of July 1937.

The unit contains 41 male, and 41 female beds. Two London Public Assistance areas are served, covering a population of over 700,000 (Pentreath and Dax).

The majority of the patients are admitted by relieving officers, and a smaller number by the police; in addition, cases are transferred directly from the chronic sick ward, or from the associated East Dulwich Hospital. Voluntary patients at London mental hospitals, who ask for their discharge and are not considered fit to be at large, are dealt with in this way, as are transfers from London County Council epileptic colonies and hospitals. Mental defectives arrive in the ordinary way, in the care of relieving officers or of the police as a result of anti-social behaviour, or in a few cases, are brought in by inspectors to the hospital as a place of safety. It is not usually desirable to certify them under the Lunacy Act and so they tend to linger; luckily they are few in number. It has been the custom to discourage the admission directly of voluntary patients.

During the period, September 1, 1938, to the end of February, 1940, 1,117 patients were admitted, giving an annual admission rate of 753. Pentreath and Dax had a total admission of 1,156 in a little over a year, and appear to have had an annual rate of 929. As opposed to this, in the year from September 1, 1937, to August 31, 1938, only 685 cases were admitted.

Cases brought in by the relieving officers or police are detained on an order which holds them for three days, or until they are seen by a magistrate within these three days. Magistrates attend on three days a week for the purpose of seeing these admissions. It is possible to present a case, with a medical certificate, to the magistrate on this first appearance, and to get an order made for his removal to a mental hospital. This summary procedure was only adopted twice during the period in question. In each case, the same man was involved. He had previously been certified at St. Francis' Hospital; he was known to be an ex-heavyweight boxer from the Irish Guards, a schizophrenic, and an alcoholic ; he had had many police convictions, and there was a long list of crimes of which he was suspected, but which could not be proved. He was, in fact, a dangerous criminal lunatic. I believe that it is only the knowledge of a previous history of such a nature which justifies immediate certification ; it apparently does not justify detention for any length of time.

In general, therefore, no order is made for removal to a mental hospital. The patient is then, for the moment, free from any order of detention, and is regarded as an inmate of an institution, and Section 24 of the Lunacy Act is invoked. By means of this, the medical officer of the institution is able to make an order, under subsection (1), for the detention of an inmate for a period not exceeding fourteen days in the institution. This is the fourteen-day order. This is the universal procedure in the London observation units. Naturally, there are a certain number who can be discharged at once before a fourteen-day order is made. Acute alcoholics are obvious cases in point. Or again, a patient may, at this moment, agree to remain for investigation, treatment, or arrangement of disposal, as a voluntary patient.

On this first appearance before a magistrate, relatives are notified by the relieving officer and advised to attend. A large number do so and an opportunity is provided to obtain a history, or for appointments to be made with the social worker. It is extremely valuable also, as the attitude the relatives are likely to adopt can be ascertained at an early date, and they can be informed of the likely outcome of the case.

This period of fourteen days constitutes, in my opinion, the *raison d'être* of an observation unit. It is a period during which observation and investigation can be carried out on the patient himself, and the history and background investigated by that essential member of the unit, the psychiatric social worker. Apart from routine physical and psychiatric examination, and any special examinations which suggest themselves, it is the custom at St. Francis' Hospital to have blood Wassermann reactions and serum bromide estimations performed on all admissions. Both are invaluable procedures.

During this time selected cases are seen by a consultant, who attends twice a week. I was fortunate in having for a considerable time the late Professor Mapother as my consultant. He once said that he attended this hospital as a consultant and not as an investigator. Perhaps, in consequence of this attitude, the work that the consultant at St. Francis' Hospital does is different from any other. He only sees selected cases : he sees as a routine all cases likely to become voluntary patients, and other cases of interest or difficulty. These cases are presented well written up, with a social history if possible, and usually with the results of Wassermann and other investigations. His visits are in the nature of a clinic, rather than a ward round. At other observation units it is customary for the consultant to see, and to write a note upon, every admission. There is an idea that, in the event of trouble arising from an error of judgment, some protection is afforded to the hospital and the medical officer. There is the other side of the question : that the medical officer has himself to make final decisions, and is frequently impelled to act contrary to the advice of his consultant. The picture may change in a few days : relatives may come forward with some alternative plan ; a greatly raised bromide level may come to light ; finally, the most eminent alienists are liable to error, and the more eminent they are, the more ready they are to admit their fallibility.

A similar procedure is adopted with cases arriving by some method other than a three-day order, except that a decision has to be made at once, whether they shall be detained on a fourteen-day order, or be made voluntary patients from that moment.

By this time, the patients have been classified, and are ready for disposal. There is

always among them a fairly large proportion of senile cases. Transient confusional attacks are extremely common in the aged. Many of them, after recovery, can go home, but many are recommended for transfer to the chronic sick ward. Unfortunately, there has been and is, in London, a very definite shortage of beds for these cases, and they tend to block the beds of observation wards. It is a mistake to press the discharge to an institution of cases in which there is any doubt about the mental condition, as they tend to be readmitted very soon. In a chronic sick hospital there is sufficient supervision for the milder degrees of dementia.

Senile cases, in general, are not sent to mental hospitals unless they are suffering from severe mental illness, or have a suicidal record. Demented cases over 70 years of age are transferred to Tooting Bec Hospital on a form of recommendation known as Form A, which avoids certification. Between the ages of 60 and 70 they are certified under Section 24 (3) of the Lunacy Act and go to the same hospital.

I have followed one guiding principle in the disposal of patients: that the mildest and most humane course possible should be pursued; certification should be avoided whenever possible and patients should be allowed to go home rather than go as voluntary patients to mental hospitals. This principle is fairly generally followed in London. A certain number of voluntary patients are sent to mental hospitals in consequence, who would be more satisfactory under certificate, and one's own readmission rate increases, but this, I feel, is better than errors in the other direction. There is an undoubted risk of suicide in a number of patients who are discharged in this way, but this is unavoidable. So far I have not had to appear at a coroner's court to answer for such an error of judgment. Some safeguard may be obtained by discharging these doubtful cases under Section 22, in which case a relative or friend gives a written undertaking to accept responsibility, and the discharge is authorized by a magistrate. This is really only a way of shifting responsibility, and I find, rather to my surprise, that I only adopted it nine times.

If a patient must be certified, the relieving officer concerned is notified and the case is again brought before a magistrate. Once more, friends and relatives are given an opportunity of attending and expressing their view. By this time most relatives, when they realize that an adequate period of observation has elapsed, and if matters have been explained to them, will accept the position, whereas earlier action would have met with violent opposition.

Of the 1,117 patients admitted in eighteen months, 96 died. Of the remaining 1,021 240 were certified by me under Section 16 and went to mental hospitals, and 27 were certified under Section 24 (3) for Tooting Bec Hospital. That is to say that only 22% of the total admissions were certified, or including senile cases sent to Tooting Bec Hospital, 24%. Voluntary patients, including admissions to the Maudsley Hospital, comprised 14% of the total. 24% were discharged to their homes. These figures correspond very closely with those of Pentreath and Dax working at the same hospital, except that their certification rate was rather higher: 28% as opposed to 24%.

The remaining patients were disposed of in various ways. The largest group is one of 86 transfers to Tooting Bec Hospital on Form A. Other destinations were institutions, convalescent homes, hostels, general hospitals, mental deficiency hospitals, epileptic colonies, and in care of the police or military authorities. Only four patients were considered suitable for temporary treatment.

I should imagine that a smaller number of temporary patients are sent from St. Francis' Hospital than from any other unit. I hope and believe that the certification rate is lower and the number of voluntary patients higher. This brings us to the question of voluntary status while in the unit itself. The normal procedure adopted when a patient is to go to a mental hospital on a voluntary basis, is that he should be seen by a consultant who signs a recommendation, the man himself signs an application, a report on the case is written, and these documents, together with a social history and particulars, are transmitted to the mental hospital concerned. If the case is accepted, and when a vacancy is available, the transfer is arranged. There may be a considerable delay before this vacancy occurs, and there may be delay for other reasons, such as the indecision or procrastination of the patient. It is therefore usual for the fourteen-day order to have elapsed before the transfer can be arranged. Before the war the Maudsley Hospital had a very long waiting list and the delay was often very long. The position arose as to the status of these patients who were awaiting transfer. Some of them, of course, would be quite unfit to wait at home. The obvious solution was to get them to sign a form expressing their willingness to

remain in the observation ward for a specific purpose, and this is what has been done. The same argument applies to cases who are waiting for convalescence or for hostels. From this, it is but a step to the introduction of voluntary status for any patient in an observation ward who is certain or likely to benefit by it, either at the beginning, during, or at the end of the normal period of detention. The Board of Control and the London County Council approve of this procedure; an approval, however, which is tempered with suspicion. The suspicion is that cases may be delayed in observation wards, which should be transferred to mental hospitals, where they can have more skilled and effective treatment. And there is a corollary: that no time should be lost in transferring an obvious lunatic to a mental hospital. Frankly, I am quite incapable of diagnosing an obvious lunatic in "the shortest possible space of time" unless I know the answer already from his history.

The period of detention which is at present allowed is the bare minimum for the adequate investigation of the average case, and it is inadequate for difficult cases. Difficult cases are common in my experience. Psychiatric diagnosis of cases going to mental hospitals, either certified or as voluntary patients, is unnecessary, usually premature, and therefore unwise.

The deciding factor is behaviour: present, past, and future. Only 38% of my cases found their way into mental hospitals and this figure would be far higher but for an adequate period for observation.

Rather than psychiatric diagnosis, the ideal for which I strove was the separation of all cases with a definite organic basis. There is a very important group which cannot be neglected in an argument of this kind. I refer to bromide intoxication. Estimations of serum bromide are carried out at the central pathological department on all admissions at St. Francis' Hospital. Minor increases were common, and 46 cases with a figure of 100 mgm.% or over were recorded, or just over 4% of all admissions. The highest estimation was 350 mgm.%. As is well known, the incidence was higher in women than in men, and in the elderly. There were eight deaths, that is 17%, but it must be remembered that many of the cases were senile subjects. Pentreath and Dax report 5% with a figure of 150 mgm.% or over, in a series of 240 cases. This suggests that recognition of the danger of bromide is increasing but slowly.

The mental symptoms in these cases were not all due to bromide intoxication. In some it was so, and their complete recovery with treatment is one of the most gratifying features of practice in observation wards. In other cases the accumulation of bromide complicated an existing abnormal mental state. It is obviously bad practice to decide the fate of these people while the picture is still clouded by some degree of bromide intoxication. These cases are difficult to diagnose clinically, and if it were not for routine examinations of the blood, a large number would be missed. The picture presented by serum bromide intoxication of delirium, confusion, restlessness and hallucination of an extreme degree, is very arresting; they are in fact the "obvious lunatics," who, it is suggested, should be transferred to a mental hospital forthwith. The gratitude of the patient and his relatives for avoiding this course is ample justification for treating them in an observation ward. My experience has been that the complete elimination of bromide in severe cases takes about a month, and I have had no hesitation in keeping them for that period of time, or longer if necessary. To quote a case in point, a woman was transferred to St. Francis' Hospital from a teaching hospital, bad offenders in this matter. Psychotic symptoms were so severe and her behaviour so difficult, that I told her doctor, who visited her, and her husband that it would be almost impossible to avoid certification. It was found that she had a serum bromide level of 350 mgm.%. She was treated, and in due course discharged perfectly well.

There is at least a possibility that similar delirious states may be caused by the abuse of other drugs, but they must be comparatively rare. I do not know of any sedative which is prescribed with the same nonchalance and freedom as bromide. However, I have met with several cases in which the psychotic picture could quite definitely be attributed to hyoscine, morphine or some compound of these with atropine. They almost invariably come from other hospitals, and are usually the result of treatment of nocturnal restlessness. These states are of brief duration, and clear up spontaneously.

Cases of drug addiction were very few, mostly morphine and heroin addicts. By the time that they reached an observation ward, their financial status had sunk so low that chlorodyne was usually the only drug available to them.

Cerebral tumours have proved to be surprisingly rare, but are naturally of supreme

importance. The gravest mistake that a psychiatrist can make is to certify a patient suffering from an operable cerebral tumour. I sincerely hope that I have not done so. Only five known cerebral tumours passed through the observation wards during the period in question. One of them is highly illustrative : she was admitted from a teaching hospital with a diagnosis of hysteria. She was transferred to a neurological hospital, and a craniotomy was performed as soon as possible, as her condition was so poor that it was considered doubtful whether she would survive for long. A subtentorial tumour was removed, and she made an excellent recovery. Had this woman been moved to a mental hospital, she would undoubtedly have perished.

I had two cases of subacute combined degeneration of the cord. One of them was seen by two neurologists and three psychiatrists, and was transferred for a time to a neurological department. Repeated blood examinations were performed. The diagnosis was disseminated sclerosis, but subsequent histological examination of his cord revealed the true state of affairs. Psychotic symptoms were variable but severe, and were of a schizophrenic nature. Unfortunately, in view of the blood picture, he was not treated with liver, and so it is impossible to prove a connexion between his psychosis and his physical condition. The second case was more instructive. A policeman was admitted in a severely psychotic state. He was extremely depressed and agitated, usually mute, refusing food, and he resisted and impeded examination. On scrutinizing his history, it was found that he had complained of vague paræsthesiæ for about a year. A blood-count revealed that he was suffering from pernicious anæmia. At this point a request was received for a report with the idea of discharging him from the force, in view of the previous reports from police surgeons who had been attending him. He was treated with injections of liver extract. His psychotic symptoms cleared up dramatically, and, when he was co-operative, the neurological condition became obvious. He was transferred to the police beds at St. Thomas's Hospital to complete his treatment, and some months later he informed me that he was back on duty.

A feature of the work in an observation unit is the occurrence of brief acute psychotic episodes. They are different types : acute confusional states of unknown ætiology ; schizophrenic episodes ; attacks of mania or depression. The picture presented differs in no way, at the time, from the psychosis that is mirrored, but the characteristic feature is spontaneous recovery in a few days, or, at the most, weeks. I believe that these transitory states are largely unfamiliar to psychiatrists whose work lies mainly in hospitals, and their frequency is not appreciated.

A report of the Board of Control suggests that every improvement of observation wards increases the temptation to undertake active treatment. I am fully in agreement that these units, at least as they are at present constituted, are no places to undertake treatment in general, but I believe that there can be very few who would seriously urge that a case of bromide intoxication or of subacute combined degeneration of the cord, should be sent to a mental hospital for treatment, or a case of cerebral tumour with psychotic or hysterical symptoms for advice.

While agreeing that everything should be done to educate the public in their attitude to mental disorder, and to mental hospitals, it is the purest folly to pretend that there is no stigma in these matters at the present time. The Mental Treatment Act has helped enormously, but relatives and patients still look askance at mental hospitals even if entry is to be on a voluntary basis. While this is so, observation units fulfil an invaluable purpose. They should reduce the number of admissions to mental hospitals and soften the blow to relatives when admission is necessary. It should be borne in mind that the majority of patients are admitted by relieving officers. I have been much impressed by the extremely conscientious and painstaking work of the relieving officers in my areas.

Deliberation involves delay, and the present organization at St. Francis' Hospital involves delay. The method of presenting cases to the consultant which has been adopted, awaiting the results of blood and other examinations, and the preparation of social histories which aim at something higher than being merely a statement by the first relative who appears, all contribute to this delay. I am convinced that it is justified, and I regard summary certification in the same light as I would summary execution. There is, in addition, another argument: there is within the London County Council a certain amount of specialization in its hospitals. St. Ebba's Hospital, for instance, takes a large proportion of voluntary and temporary patients and others of a particular type, and cases of general paralysis were concentrated in Horton before the war, and now, Long Grove. It is essential that time should be allowed to sort out these cases.

It might be thought that all cases of general paralysis could be sent at once to the appropriate hospital, and indeed this has been done when the diagnosis has been certain. But I have been surprised by the proportion free from all neurological signs, and with psychoses not remotely suggesting general paralysis of the insane. These cases are only revealed by routine blood, and subsequently cerebrospinal fluid, examination. The number of cases of general paralysis of the insane was 28 or only 1.6%. This compares with approximately 3% of Pentreath and Dax.

Only four patients were considered suitable for temporary treatment. The reason is, that on admission a very large number could be deemed to fulfil the necessary conditions, but after a period of observation, they nearly all recover volition. A few must then be certified, which would have been their eventual fate anyhow, but the majority are discharged or become voluntary patients. Pentreath and Dax arrived at exactly the same conclusion. I have heard it stated that in the best interests of the patient the conditions of this Section of the Act may well be stretched to a certain extent. I feel that one is more justified in pressing for voluntary treatment.

Alcoholism presents special and interesting problems. Of my series, 96 showed evidence of alcoholism, or a history of alcoholism was obtained. Pentreath and Dax give a figure of nearly 10%. It is interesting to note that in the first month of the war, I only admitted one alcoholic, a case of Korsakow's psychosis, with, naturally, a very prolonged history. The absence of acute alcoholism was remarkable. During September, October and November, the percentage was 5%, being definitely below the previous level, and this fall has been maintained. The high percentage of alcoholics admitted to this unit is interesting, as it is the general opinion that the alcoholic psychoses are few in number and that they are decreasing steadily. Figures for alcoholism in general, obtained from the population of mental hospitals supplied with these admissions from observation wards are obviously valueless; the filter has been in action. Curran in the *British Journal of Inebriety*, July 1939, states that of 600 consecutive patients, seen in the psychiatric outpatient department of St. George's Hospital, only four were alcoholics (0·6%). The percentage was even less at Maida Vale Hospital. However, among 600 patients seen in private there were 34 alcoholics (6·6%). He says that if any conclusion can be drawn it is that inebriety is becoming increasingly the prerogative of the more well-to-do sections of the community. This contention obviously cannot be maintained.

Cheap wine drinking has been the subject of more than one investigation. Dr. Letitia Fairfield kindly allowed me to read a report of hers on the subject, and there is an extensive report by a Select Committee of the Government of Northern Ireland on adulterated wine, published in 1938. These investigations were prompted by the increasing number of cases appearing in the police and other courts, and the subsequent comments from the bench, and in the press.

Wine drinking was not popular or widespread in Great Britain before the war of 1914-18. It started in Glasgow about 1920, and was probably due to the great increase in the price of whisky; it then spread to all parts of the United Kingdom, but has been confined almost exclusively to the large towns. The wine was originally red Lisbon wine, but this was largely replaced by wine fermented in this country from imported juice. For the last ten years Australian white and red wines have almost monopolized the market, although there is a big sale of wines produced in this country and called "Port type" or "Sherry type". The popular name, Red Lizzy, would seem to be derived from Lisbon, and other names have followed: Red Biddy, Tony (Tawny) wine, Dido, Johnny Jump Up, Finish. My one contribution to this list is Lunatic Broth.

There is considerable confusion about the use of these names. Red Lizzy is popularly supposed to be red wine adulterated with some other spirit, usually methylated spirit, and that such mixtures can be bought by initiates in certain low-down premises. Absolutely no evidence has been obtained of the sale of adulterated wine. There is frequently evidence, however, that individuals buy this wine, and themselves mix with it, usually methylated spirits, but also such alcoholic liquids as eau-de-Cologne or lavender water. There is, therefore, no case for investigation from the licensing or excise point of view, except for the control of the sale of methylated spirits. Nevertheless, there is undoubtedly a serious social problem to be faced. I can offer no evidence that there is anything intrinsically harmful in these wines, but little is known about the different effects of mature and immature alcoholic drinks, and these are naturally immature. I am convinced that the secret of the whole thing lies in the price. Speaking of pre-war prices, it was possible,

in certain establishments, to get a pint of wine for a shilling, although the price is variable. These wines vary in alcoholic strength from about 15% to 20%. Comparing this with beer at 8d. a pint, with an average strengtn ot 5% to 6%, it is at once evident that a very much greater amount of alcohol can be obtained, for a unit of money, in wine. The same thing applies to spirits, and these wines are actually the cheapest form of alcoholic drink. Addicts, however, will drink this wine in the same quantities in which they are used to drinking beer. Apart from this, I have gained the impression that habit formation is particularly strong, and that anorexia is common and early.

It is well recognized that alcoholic neuritis is caused, not by the alcohol itself, but by a deficiency of vitamin B_1. In May 1939, in a discussion at the Royal Society of Medicine on the clinical aspect of vitamin B_1, Carmichael stated that he had, some years back, circularized the London County Council general hospitals asking for cases of alcoholic neuritis. I cannot remember whether he said that he got one case or two; from this, he inferred that the condition is rare in England. Actually, I was rarely lacking in at least one case of neuritis. A gross dietary deficiency could invariably be demonstrated, when any history was available. An extreme case was that of a woman whose diet for three months had been known to consist of beer and whisky, and, on one occasion a plate of jellied eels. Among other investigations into these cases, I was lucky in being able to have blood vitamin B_1 estimations on certain cases. The value in the severe chronic cases was significantly low. The immediate treatment of these cases is satisfactory for the immediate condition, and most unsatisfactory for the future. As the late Professor Mapother put it in the Norman Kerr lecture for 1938 to the Society for the Study of Inebriety, in addiction treatment is a matter of supervising nursing until the patient is ready to start drinking again. The immediate treatment with large doses of vitamin B_1 either by mouth or by injection is very successful. Certification is of little value as the patients cannot be held after they have recovered from the acute phase. The most satisfactory treatment is as a voluntary patient for a period of two years.

To return to the observation unit system, these wards should be part of, or closely attached to, a general hospital. When a surgical, medical or pathological opinion is required consultants of all kinds should be readily available. I think that the ideal would be if they were attached to teaching hospitals. The reason for this is that the cases in an observation unit are ideal for teaching students. They are in fact just those cases with which the medical student will shortly be faced in practice. There is a difficulty in the ideal location of these units; they should be attached to a general hospital, but at the same time it is absurd to expect them to be free from noise. The patients are there for observation of their mental states, and not for interesting drug reactions. Padded rooms are even more useful than paraldehyde.

Apart from their use for the teaching of students and of post-graduate students, which is far from being exploited to the full, these hospitals provide unique material for research which is practically untapped. The ideal arrangement would be for a senior medical officer to be appointed, together with a junior who had recently joined the service; in fact, it might be a condition of appointment that he should be liable to a period of work at an observation unit. The experience would be invaluable. In the same way, a period of duty at one of these units for nurses would improve the standard of nursing at the unit and be of value to the nurse.

There is a lack of liaison between the units and the mental hospitals, due partly to the fact that they are run by different departments of the London County Council, and partly because each unit has to send cases to several hospitals and so cannot develop close relations with any one hospital to the exclusion of the others. A possibility is the formation of fewer and even larger psychiatric centres, which could have representatives from all the hospitals. Apart from their function as observation units, these centres might well undertake more active and urgent treatment.

No discussion on such a subject can well be closed without at least a mention of the law. When a patient goes to a London County Council mental hospital as a voluntary patient, puts in for his discharge, and is considered to be unfit to be at large, or at his home, it is very rightly considered undesirable that he should be certified in that hospital. The correct procedure would be to call in a relieving officer and have him removed to an observation ward. The objection to this quite legal method is that the London County Council Mental Hospitals are mainly situated in th counties, mainly in Surrey.

A Surrey relieving officer would therefore have to be called, and the patient removed to a Surrey observation ward. There he might be certified and transferred to a Surrey hospital. Later, as he is chargeable to London, he would have to be moved to a London hospital. In order to avoid these complications, these patients are transferred to London observations wards, on no order at all. On arrival, they must be placed on a fourteen-day order, or made into voluntary patients, or even discharged. In practice, many difficult situations arise. For a time, I was considerably exercised about the illegality of this procedure, although it was carried out in the best interests of the patient. Later, however, it occurred to me that the whole of Section 24, so widely used, is no longer applicable to observation units. The relevant subsections of this section provide for the detention of an inmate of an institution, in that institution, for fourteen days or permanently, and for the instruction of a relieving officer to bring such an inmate before a magistrate with a view to certification. These orders must be signed by the medical officer of the institution. I strongly suspect that there is, in the law, only one medical officer, and he is the medical superintendent. I am quite sure that the present units, or at least some of them, are not parts of institutions, but are very definitely hospitals. Further, when Section 24 (3) is used, an order is made for the detention of the inmate in the institution in which he happens to be. In practice, he will shortly be moved to Tooting Bec Hospital. If my reading of the position is correct, it would seem that the law is completely out of date, and therefore there is no need to worry about any questionable procedure, such as the presence of voluntary patients in an observation ward, provided that one is convinced that one is doing the best for one's patient.

If Section 24 of the Lunacy Act is illegally used in observation wards, I fail to see how it can be used at all, even illegally, when direct admission to a mental hospital is employed, unless of course such mental hospital has a workhouse or institution attached to it. This would seem to imply that a decision must be made in every case within three days, possibly sometimes within a few hours.

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Discussion.—Dr. IAN SKOTTOWE: It is necessary to make a clear distinction between observation units which are the modern development of the old workhouse observation wards of a generation ago and observation units which are essentially planned as psychiatric filters or centres for special investigation associated with general teaching hospitals.

I am not quite clear what Dr. Butler means when he refers to large, plentifully staffed psychiatric centres, which he places beyond the scope of this discussion. According to him the dividing line between these and observation units proper is determined by whether or not treatment is undertaken, and I assume, therefore, that in this excluded group he would place such establishments as the Maudsley Hospital, Jordanburn, the Boston Psychopathic Hospital, the Burden Neurological Institute and the Park Hospital, Oxford. It is impossible to divorce investigation from treatment. Investigation *is* treatment—as those who deal exclusively with psychoneuroses constantly emphasize. The state of a mentally ill patient is modified to a greater or less extent by every experience which befalls him, and while one can well understand the eagerness of those psychiatrists who crave objectivity at all costs, it is well to pause before unleashing the army of specialists of all kinds, the extolling of whose value is becoming a trifle threadbare in psychiatry, upon the hapless, sensitive, emotionally upset patient who not only finds himself in new and strange surroundings but quite probably hardly an hour or a day passes but someone puts needles in his veins or back, a tube down his throat, flashes lights in his eyes or even clasps his body and head in the tender embrace of the newest electrodes.

No doubt all these devices will add to our knowledge—relevant or otherwise—and if they happen to be relevant some of them may even assist towards the cure which is our aim; but unless we are to regard the early case practically as pure research fodder I submit that it is absolutely wrong to embark on wholesale routine investigation of this kind except step by step with the most carefully planned scheme of general management of the individual case, as well as a general plan of therapy based, from the start, on careful initial clinical examination by a general psychiatrist. There is a regrettable tendency to run away from the clinical situation, and the blessed word " investigation "

should not be used as evasion of the need for accurate clinical examination, appraisement of the significance of the facts observed and the making of and acting upon a quick decision in the same way as physicians in other branches of medicine must do, devoid as they are of the administrative and legal camouflage with which it is so easy to envelop the psychiatric case. To speak of "nervous breakdown" when we mean melancholia or schizophrenia as the case may be, and to suggest the sending of such a patient to some place "for observation", when we know—or ought to know—that we are facing an illness that is going to be of many months' duration and is in the long run going to call for all the therapeutic resources that an ordinary mental hospital, and only an ordinary mental hospital, can produce, is not only dishonest, it is pandering to public prejudice, and by reason of double removal or transfer from one place to another, with the awful spectre of the mental hospital looming on the horizon as the very last resort, there may be—and in many cases is—a severe emotional blow which, together with his experiences in the observation unit, puts the patient in such an unco-operative frame of mind that future management is rendered extremely difficult and medical treatment seriously hampered.

In the light of these considerations the doctrine of removal to a mental hospital only *after* the fullest possible investigation begins to assume a different perspective. Would it not be better to adopt a policy of reliance upon initial clinical examination and then, if clinically indicated, removal to a mental hospital *for* the fullest possible investigation which can take place under the controlled direction of the physicians who can undertake and plan treatment from the start?

In my submission this is the correct policy, but I recognize that it carries with it an obligation on the part of the mental hospitals to provide really satisfactory means of classification, staffing and access to the use of the full forces of other branches of clinical and laboratory work as and when required.

I submit these observations not as a hypothesis, but out of practical experience of working the arrangements which I now suggest in both a borough and a county over a period of nearly ten years. I refer to Swansea and Buckinghamshire, where there are no observation units at all, but where the services of members of the mental hospital staff are available to assist practitioners, public assistance authorities and general hospitals as required. The fact is that both in the degree to which the Mental Treatment Act is operated and in their useful discharge rates, the mental hospitals of these two very differently circumstanced authorities will stand comparison with any. Lest there be any misapprehension, it can at once be said that this is by no means only a personal experience, as the accompanying representative figures embodying both counties and boroughs in widely varying circumstances will show.

1938

Mental hospital	Total admissions (excluding transfers)	Admissions via public assistance institutions or public health hospitals
Bucks	241	45
Swansea	271	44
Carmarthen	158	5
Cornwall	201	20
Dorset	246	13
Knowle	318	37
Leicestershire and Rutland	163	32
Monmouth	203	29
Norfolk	243	25
Isle of Wight	113	5
Barnsley Hall	152	19
North Riding	216	25
Exeter City	64	2
Leicester City	216	36
Portsmouth	323	36
	3128	373 = 11·9%

If fifteen representative areas can show that 88% of their admissions to the mental hospitals come direct from their own houses, there seems to be little strength in the case for the continuation of the observation unit and one is forced to answer the question "Cannot this residue of 12% (not all of which represent cases of difficulty, for some of them are psychoses which have developed in the ordinary public assistance population) be better dealt with by raising (*a*) the medical standards of clinical psychiatry and (*b*) the architectural standards of the mental hospital?" There is no case at all for the continuation of public assistance observation wards, especially in the light of the

survey which was made by the Board of Control in conjunction with the Ministry of Health in 1935, the results of which are succinctly and cogently put in the Twenty-second Annual Report of the Board of Control for the Year 1935 (p. 7). It may be possible to to make out a case for the pure research type of unit associated with and architecturally linked to a teaching hospital. These are necessarily debarred from receiving cases presenting gross conduct disorder, and their use is thereby severely limited. They should, I think, receive only specially selected cases referred either from the out-patient department or from the mental hospital. But they are unsuited for use as the routine channel by which the ordinary psychiatric case reaches the mental hospital or as a filter by which it is prevented from doing so. Even for teaching purposes such units can show only a very limited facet of the psychiatric field, but they may be of great value in the knowledge that research workers may gain through them. I cannot imagine, however, that with proper organisation, staffing and interaction with other regional medical institutions such a unit could not equally well form part of a mental hospital.

Mr. R. H. CURTIS, O.B.E., Chief Officer of the Mental Hospitals Department, L.C.C., speaking as an administrative officer, pointed out that the arrangements which obtained in London, as described by Dr. Butler, were calculated specially to meet the needs of London, with a large number of mental hospitals, some with a certain specialization of function, and a central system of allotting beds to patients. The alternative method of direct admission to the mental hospital might better suit the needs of a County or Borough with one hospital. The London scheme provided for close association between the observation units and the mental hospital service by means of the provision from the latter of experienced medical officers seconded to take charge of the units and of senior medical officers to act as visiting psychiatric consultants.

Lt.-Col. A. A. W. PETRIE, in summing up, said that he would have like to have dealt with many of the minor points raised, particularly with the desirability of allowing direct admissions to the mental hospital when this was wished by the relatives and the doctor of the patient. Dr. Butler had stressed the fears of patients and their relatives in regard to their entering mental hospitals. He himself felt that until all recoverable cases were dealt with away from the chronic insane, such prejudice would exist. Even then the relatives of those whose conduct was disordered would deprecate the patient being put with others like himself. The principal fear, however, was entering an institution some of whose inmates had been under care for many years.

The development of the present very imperfect observation ward into a proper psychopathic hospital such as those seen in Germany and the United States of America was the obvious development needed, it would cost little more, and would render a great service to the community. Various schemes had been evolved, and a British Medical Association Committee was shortly reporting on the matter. The development of proper psychopathic hospitals would not alone solve the problem, as many cases could not be kept there until recovery. Units administered from, but not in the grounds of the county mental hospitals would provide such accommodation.

This would allow the staff of the mental hospital to deal with recoverable cases, while preventing the patients from feeling they were being treated among the chronically insane.

In any case, there should be interchangeability with the staff of the mental and psychopathic hospitals, and also with any university clinic available.

Section of Obstetrics and Gynæcology

President—W. GILLIATT, C.V.O., M.S.

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Radio-Opaque Calcification of the Fallopian Tubes with Tubal Patency

By STANLEY A. BOND, M.B.

(*By Courtesy of Mr. Leslie Williams and Dr. S. Cochrane Shanks*)

CALCIUM (psammoma) bodies in the fallopian tubes were recognized in the oldest pathological textbooks and were often regarded as absolute evidence of healed tuberculosis while radio-opaque calcification in the tubes has been shown before (Bârcá, 1932), but the following case shows special features.

The patient, a radiographer, complained of intermittent attacks of dull pain in the right iliac fossa for two years. This pain travelled down the right leg and went to the

Radiogram showing calcification in the fallopian tubes.

umbilicus during one acute attack and was then followed by vomiting. Listlessness was present for one year. Her bowels were regular.

A diagnosis of appendicitis was made and this was confirmed by X-ray after a barium enema. Quite by accident it was discovered that the fallopian tubes and uterus were clearly visible on the film and that a true outline of the tubes with convolutions was present.

The gynæcological history revealed that the menstrual flow was scanty and the periods were often seven to twelve days late. There was no dysmenorrhœa and no complaint of vaginal discharge.

Previous history showed that tuberculous peritonitis had occurred sixteen years ago

when she was in bed four months and was treated with ultra-violet light and intramuscular iodine injections. At that time there was a question of involvement of the right lung.

The patient was admitted to hospital for insufflation of the fallopian tubes. At first no gas passed through the tubes, then when a manometer reading of 200 was reached for the second time the pressure suddenly started to fall in a slow, jerky, "staircase" manner and when the insufflation was repeated several times the gas eventually passed through easily at a pressure of 100. On auscultation the left tube only seemed patent.

On laparotomy a definitely diseased retrocæcal appendix was found and removed. A large calcareous plaque was present on the fundus of the uterus and both tubes were bound down by adhesions in the pelvis along their full length and at their fimbriated extremities. Some of the adhesions were freed round the left tube but very little operative interference was undertaken.

Calcification may be found in any tuberculous salpingitis undergoing healing but sometimes the process goes beyond calcification to one of actual ossification and bone and marrow have been found together (Lehmacher, 1916).

It does seem surprising that tubes so diseased should be patent but "on microscopical examination of a tuberculous tube one is struck with the absence of agglutination of the mucosal folds and exudative material seen in the banal types of salpingitis" (Jameson, 1935) and it would seem that in this case it was mainly the serosal layer which was affected so that the adhesions broken down on insufflation were probably around the abdominal ostia of the tube.

As the patient has just been married an ectopic pregnancy must be regarded as a possible complication and such cases have been reported (Busby and Fisher, 1940).

In a series of 37 cases of tuberculous salpingitis observed by one man sterility was noted in 85·6% of cases and the recorder goes on to say that "it is probable that the woman who develops tubal tuberculosis will henceforth be sterile and that any pregnancies listed in her history occurred before the disease appeared" (Jameson, 1935), but pregnancy can occur, though the ovum may be arrested in its passage along the tube, and indeed full-time pregnancy has been noted in a case of early double tuberculous salpingitis (Schröder and Rau, 1920).

As a therapeutic measure, the disease being now inactive it might be well worth while instilling iodized oil into the tubes with a view to absorbing adhesions and thus increasing the chance of normal pregnancy, but the value of this measure is problematical.

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Brain Showing Cerebral Hæmorrhage in a Case of Spontaneous Labour

Professor F. J. Browne showed the brain of a child aged 4 days in which there was a clot about 1½ in. long in each lateral ventricle. The mother, aged 27, had two previous miscarriages at mid-pregnancy. When seen before the third pregnancy no abnormality could be found except chronic hypertension, the blood-pressure being 140/80. When she became pregnant for the third time she was under regular care and, as often happens in these cases, a flare-up occurred in the 28th week with increase of blood-pressure, albuminuria and some œdema. Nevertheless the pregnancy was carried on successfully until the end of the 36th week when it was intended to carry out Cæsarean section. The fœtus, however, was small—judged to be under 4 lb. and so it was decided to delay for at least another week. Five days later she went into labour and with two or three pains a child 4 lb. 8 oz. was born. The membranes were intact until the head reached the vulva and were then ruptured artificially. The child, judging by its weight, should have done well but it developed intermittent attacks of cyanosis, fed badly and died on the fourth day. The cause of death was the hæmorrhage in both lateral ventricles. Professor Browne's practice in cases where a chronic nephritic or chronic hypertensive woman had been successfully carried to term or near it is to do Cæsarean section for the sake of the child as soon as it was large enough to have a chance of survival. In his opinion the case shown afforded strong support for this practice.

Chronic Nephritis in Pregnancy

By Gladys H. Dodds, F.R.C.S., and F. J. Browne, M.D., F.R.C.S.Ed.

Chronic glomerular nephritis is predominantly a disease of young people, yet it is rarely associated with pregnancy. When it does occur the complication is a grave one for mother and child.

The literature on chronic nephritis and pregnancy is extensive but is usually confusing, as chronic hyperpiesis is often included under the term chronic nephritis. From our observations over a period of fourteen years at University College Hospital we are convinced that the course and prognosis is entirely different in these two conditions. Wellen, (1940) in a recent paper on pregnancy toxæmias, classified his cases of hyperpiesis and chronic glomerular nephritis separately. Only four of his patients had chronic glomerular nephritis, an incidence of 1 : 2,000 deliveries. In the last fourteen years we have observed 17 patients with chronic glomerular nephritis in 21 pregnancies, an incidence of 1 : 1,100 deliveries. Of the 17 patients, 9 were primipara and 8 multipara. Of the multipara, 5 were para 1, 2 were para 2, 1 was para 3. Of the babies who survived 5 were firstborn children.

The pathological picture of chronic glomerular nephritis varies with the time that has elapsed between the onset of the disease and the death of the patient.

Diagnosis

A clinical diagnosis of chronic nephritis complicating pregnancy presents many difficulties. It is necessary sometimes to keep the patient under observation over a long period of time before we can be certain of the diagnosis. One of our patients passed through two pregnancies and was followed up for six years before we obtained *conclusive* evidence that our original diagnosis was correct. It is hardly ever possible to make an immediate diagnosis if the patient is seen for the first time after the 20th week of pregnancy. When we see the patient for the first time before she is 20 weeks pregnant the diagnosis is made from the history of pre-existing nephritis, the clinical examination of the patient and the results of various tests of renal function.

History of pre-existing nephritis.—In the present series this was obtained from 11 of the 17 patients. The history they gave *is* reliable since several had been under observation in the medical wards at University College Hospital, and we obtained the hospital records of the remaining patients who had been treated elsewhere. Six patients gave no history of pre-existing nephritis; two had had scarlet fever and one had had frequent sore throats.

Clinical findings.—The age of the patient is of interest. Eleven (65%) of the 17 patients were below the age of 25. Chronic glomerular nephritis is a disease of all ages but predominantly of the earlier periods of life. That it is so rarely associated with pregnancy is therefore striking. It is of interest to note that 71 (49%) of our 144 patients with pre-eclamptic toxæmia were below the age of 25, while only seven (11%) of our 65 patients who had hyperpiesia complicating pregnancy were below the age of 25.

Albuminuria was found at the first visit of all the patients; frequently the amount was only a trace. At some time during the pregnancy microscopic examination of the urine showed epithelial cells, red blood-cells and hyaline and granular casts.

Œdema is rarely present in early pregnancy and was only met with twice in our series before the 20th week.

Heart.—Enlargement of the heart was found in only one of these 17 patients. This patient had advanced chronic nephritis.

Blood-pressure.—The blood-pressure ranged between 114/72 and 190/130 mm. Hg. A comparatively low blood-pressure is one of the features that help us to diagnose chronic nephritis from hypertensive toxæmia.

Fundus oculi.—Only two of our patients had albuminuric retinitis and both these had advanced chronic nephritis. The absence, therefore, of retinal changes does not exclude mild or fairly severe degree of chronic nephritis.

Renal function tests.—Chemical tests of renal function are in general only of diagnostic value in patients with an advanced degree of chronic nephritis. Our investigations have shown, however, that chronic nephritis should be suspected when the blood urea is over 40 mgm. per 100 c.c., when the urea clearance is below 60% of the normal and when the urea concentration test is under 2 grm. %. It must be emphasized that normal renal function as revealed by chemical tests is compatible with the presence of chronic nephritis of the milder degrees.

Thus on clinical examination of a patient with chronic nephritis in early pregnancy the only abnormal finding may be a persistent trace of albuminuria.

Differential Diagnosis

(1) *Chronic nephritis* requires to be differentiated from other *renal conditions where albumin is present in the urine* such as pyelitis, calculus and tuberculosis. This is done by microscopic examination of the urine, culture, guinea-pig inoculation and X-ray examination. (2) *Anæmia,* especially the macrocytic type, may cause albuminuria but it can be excluded by a blood-count. (3) *Functional albuminuria* does not present a serious difficulty. Albuminuria in this condition, if it exists, disappears when the patient is put to bed and red cells and granular casts are consistently absent. (4) *Lordotic albuminuria* is not present before the 20th week as before that time there is no lordosis. (5) *Hyperpiesia* can be differentiated before the 20th week of pregnancy. The blood-pressure is usually higher than in chronic nephritis. There is no albuminuria and kidney function tests are normal. After the 20th week the same remarks apply unless so much exacerbation of blood-pressure has occurred as to cause œdema and albuminuria. In such a case diagnosis cannot be made until the patient is followed up after delivery, sometimes for a period of six to twelve months or even longer. (6) *Pre-eclamptic toxæmia.* In this case the blood-pressure is not raised and there is no albuminuria before the 20th week, except in very rare cases, e.g. vesicular mole. If the patient is seen after the 20th week a diagnosis cannot be made until after delivery.

Course and Prognosis

These patients often undergo an exacerbation of symptoms during pregnancy. 47% of our patients did so. Albuminuria then increases, œdema appears if it has not been already present or increases if it has and the blood-pressure usually rises. The blood urea is apt to increase and in severe cases albuminuric retinitis may appear. Intra-uterine death of the fœtus may occur or miscarriage or premature labour on account of placental damage.

It is usually stated that exacerbation of the nephritic condition tends to occur earlier in each successive pregnancy. While this is probably so we are unable to confirm or refute this from our own experience.

It is interesting to observe that nine (53%) of our 17 patients went through their pregnancies without any sign of deterioration. One of these was a patient in whom decapsulation of both kidneys had been done in University College Hospital six years before for acute nephritis. At the beginning of her first pregnancy there was albuminuria with normal blood-pressure and no other physical signs. This patient has carried two children to term (the last baby weighed 7½ lb.), and in neither pregnancy was there any increase in the albuminuria or other evidence of deterioration.

Prognosis for the fœtus.—There is a serious liability to intra-uterine death when exacerbation of the nephritis takes place. The immediate cause of intra-uterine death is placental infarction. It is probable that if more than half the placenta is infarcted the fœtus will die *in utero.* Where the fœtus survives to term it must be expected that it would be smaller than normal. This is of great importance when the question of terminating pregnancy by Cæsarean section or otherwise is concerned, because at the end of the 36th week, when in a normal pregnancy the child usually weighs 6 lb. or over, it may in chronic nephritis weigh 4 lb. or less. Its vitality is also low and its resistance to infection poor. In the 21 pregnancies observed 13 babies (62%) were born alive and survived.

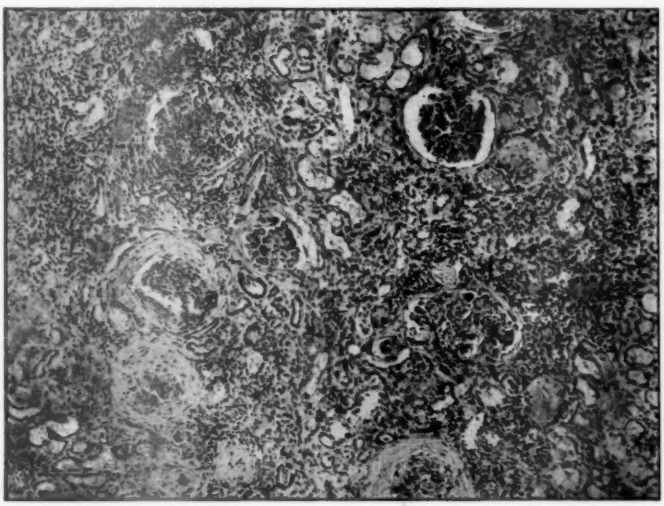
Remote prognosis for the mother.—This is usually regarded as extremely unfavourable. Stander, in his ten-year follow-up of chronic nephritic patients found that 42·5% were dead at the end of this time. Our experience is almost equally unfavourable. Six of the 17 patients are dead (33%). The patients were followed up for a period varying from six months to twelve years. In addition to the six patients who have died two other patients have reached the closing stages in the drama. They have passed from the stage of persistent albuminuria to uræmia, extreme hyperpiesis and albuminuric retinitis—one six years and one two years after her pregnancy. Over half the patients did not seem to be any the worse for their pregnancies.

It must, however, be noted that chronic nephritis is a progressive condition and we are not prepared to state that the deterioration seen in 47% of our cases was caused by the pregnancy, although we have no reason to say that it is not.

Post-mortem examinations were made on three of the six patients who died and sections of these kidneys have been available for study. All showed chronic glomerular nephritis. We are indebted to Professor Barnard of St. Thomas's Hospital for the following description of the kidney section illustrated.

E. G., aged 29, Para 0. No history of previous illnesses. Present pregnancy—œdema of vulva and legs at 19th week of pregnancy. She was under treatment by own doctor until 32nd week of pregnancy when she was admitted to hospital. There was marked œdema of legs, vulva, abdominal wall, hands and face. Urine—albumin 5%. Hyaline and granular casts, red blood-cells. Slight œdema in right fundus oculi. Blood-pressure 132/92 mm. Hg. Blood urea 42 mgm.%. Urea clearance 18% of normal. Urea concentration test 1·5 grm.%. She was delivered at 35th week of a 3¼ lb. female infant, who survived. This patient was kept under observation until her death five and a half years later. She had albuminuria which gradually increased in amount, her blood-pressure rose to 176/110 mm. Hg. She developed a marked secondary anæmia, colitis and finally uræmia.

Report on kidney section stained hæmatoxylin and eosin and van Gieson.—257/37. There is a severe chronic inflammatory infiltration by lymphocytes, plasma cells and an occasional neutrophil leucocyte. This infiltration is concentrated in the labyrinths (i.e. the region of the glomeruli and convoluted tubules). Throughout the kidney there is a diffuse fibrosis which is most conspicuous between the labyrinths. The chronic inflammatory infiltration extends into that part of the medulla nearest to the cortex.



The glomeruli are severely affected; none in the section are normal. Those least affected have fibrosis of the capsule and most of these have in addition one or more adhesions to the capsule. The glomeruli most severely affected are represented by small tufts of fibrous tissue. The bulk of the glomeruli are in stages intermediate between these two: focal patches of necrosis, fibrosis of a part or of the whole of the tuft and fibrous thickening of the capsule, forming the chief changes.

The tubules in the labyrinths are for the most part atrophied but occasional groups both in the labyrinths and between them are hypertrophied and dilated.

In the medulla some tubules contain structureless material stained pink with eosin, some pus and pink material.

The appearance suggests a chronic toxic nephritis in which the maximum damage has been borne by the glomeruli (*see* illustration).

Treatment

If it is true that pregnancy is always liable to cause an exacerbation of the disease and shorten the patient's life it is obvious that the best course to adopt is to terminate the pregnancy as soon as the condition is diagnosed—which is generally before the fœtus is viable. It is nearly always advisable to carry out sterilization at the same time or shortly afterwards. The method to be adopted depends on the stage of the pregnancy:

abdominal hysterotomy if the pregnancy is less than twelve weeks; induction of premature labour if later than the 12th and not yet at the 36th week, and Cæsarean section if at the 36th week or after. While this is the standard treatment there are exceptions. One not infrequently meets with a patient who badly wants a child and prefers to continue the pregnancy, and if the nephritis is mild in degree her wish may be acceded to. If, however, the nephritis is of severe degree as shown by high blood urea—over 40 mgm. per 100 c.c. albuminuric retinitis, much albumin and œdema—the prognosis is so bad for mother and child that the pregnancy should not be allowed to continue. We have already seen that in the mild cases a patient may go through her pregnancy without any serious disturbance and produce a living child without being apparently the worse. What can be done for those patients in whom, after due consideration, the pregnancy is allowed to continue? It is advisable that the patient should be kept under observation, preferably in an institution. She need not stay in bed constantly unless there is a tendency for the blood-pressure to rise or the albuminuria to increase. This usually means that she must be kept in bed from the 25th week onwards when exacerbation generally occurs if it does so at all.

Diet, chiefly vegetarian with no butcher meat, should contain a liberal supply of fresh green-stuffs, milk and other dairy produce. We give all these patients vitamin B either in the form of marmite or bemax and vitamin D in the form of halibut liver oil. A hæmoglobin estimation is done at the beginning of pregnancy and at intervals thereafter and if necessary iron is given. We have had good results with three fersolate tablets daily, but in our experience the anæmia associated with chronic nephritis does not respond well to iron and we have had sometimes to use blood transfusions in addition. Occasionally the patient refuses to stay in hospital and she should then be warned about avoiding fatigue and of the dangers of exposure to cold and wet, which seem to precipitate an exacerbation.

The longer the pregnancy continues the greater is the liability to fœtal death and therefore it is advisable to consider termination of pregnancy at the end of the 36th week. It must always be remembered that the fœtus may be considerably smaller than it should be for the period of pregnancy and that one should make as certain as possible that the child is at least 4 lb. in weight before the pregnancy is terminated. In many cases on account of placental infarction the child has not reached 4 lb. at the end of the 36th week and termination must, if possible, be postponed until it has. In estimating the weight of the fœtus several points must be taken into consideration: (1) Height of the fundus; (2) abdominal girth; (3) size, hardness and maturity of the fœtal head by abdominal and vaginal palpation. Considerable assistance may be obtained from cephalometry in which the biparietal or occipito-frontal diameters are measured and the weight of the fœtus estimated therefrom.

The margin of error in deducing weight from head measurements is a very wide one and while cephalometry is of value, and should always be used, it is of limited helpfulness and must be regarded as complementary to the clinical examination.

Method of terminating pregnancy if child is viable.—We believe that in every case Cæsarean section by the classical method should be carried out because of the danger to the child of cerebral hæmorrhage. Whether the patient is sterilized at the same time must depend on circumstances which vary in each case. It must be emphasized that Cæsarean section is being done for the sake of the child and not in order to allow sterilization to be carried out.

Conclusions

(1) Chronic glomerular nephritis is a rare complication of pregnancy. The incidence during the last fourteen years at University College Hospital was 1 : 1,100 deliveries.

(2) The diagnosis of chronic nephritis in pregnancy is difficult. The differential diagnosis from pre-eclamptic toxæmia and hyperpiesis when the patient is seen after the 20th week of pregnancy often cannot be made until six to twelve months or longer after delivery.

(3) Outlook for the fœtus: In our series 13 infants survived from 21 pregnancies (62%).

(4) The remote prognosis for the mother is bad. The mortality in our series is six out of 17 patients (33%). In addition two patients are much worse since their pregnancies. In all therefore eight (47%) have either died or become worse after delivery.

(5) Termination of the pregnancy as soon as the condition is diagnosed is usually the best treatment from the point of view of the mother's expectation of life.

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Section of Otology

President—T. RITCHIE RODGER, M.D.

[*May* 3, 1940]

The Mechanism of Acustico-Lateral Sense Organs in Fishes, with Special Reference to Problems in the Physiology of Semicircular Canals

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THE physiology of the vertebrate labyrinth has been concerned mainly with two problems: the description of the reflexes that are evoked by various forms of stimulation, and the definition of the localization of function within the labyrinth and the mechanism of excitation of the separate labyrinthine end-organs. Concerning the function of the otolith organs there is still considerable uncertainty (Huddleston, 1928; Werner, 1929: Hasegawa, 1931, 1935; de Kleijn and Versteegh, 1933), but the role of the semicircular canals in the liberation of the dynamic reflexes of eyes and limbs in response to angular displacement of the head is now firmly established (McNally and Tait, 1925, 1933; Huizinga, 1931, 1932, 1935). There remain, however, a number of controversial problems. Elimination experiments have failed to disclose the precise part played by each semicircular canal in the reflexes to rotation about the three primary axes, and the way in which the six canals co-operate in discriminating any given axis of rotation. Opinion is divided between those who believe the two anterior vertical canals to work together in antagonism to the two posterior canals, and those who claim that there is a diagonal synergy, the anterior canal working in co-operation with the contralateral posterior canal. Huizinga (1932) adheres to the latter view.

Following the work of Ewald (1892), numerous authors have brought forward evidence that the semicircular canals have an important share in the influence which the labyrinths exercise over muscle tone (Maxwell, 1923; Lorente de Nó, 1926; Huizinga, 1932, 1935; Tait and McNally, 1934; Löwenstein, 1937). The nature of this influence has, until recently, found no clearer interpretation than is implied in Huizinga's phrase "eine gewisse Spannung in den Cristae".

Several workers have observed that, following unilateral extirpation of the labyrinth, the appropriate reflex responses of the eyes may yet occur in response to rotation in either direction, and Lorente de Nó (1931) is of the opinion that ampullopetal and ampullofugal flow of endolymph produce reflex effects of equal magnitude. The Mach-Breuer theory of the mechanism of the semicircular canals provides no clue to the possible basis of such sensory discrimination.

The most striking effects of prolonged horizontal rotation are the nystagmus and after-nystagmus that occur at the beginning and end of rotation. The duration and intensity of these reflexes have been shown to be related to the duration and velocity of rotation (Maier and Lion, 1921; Masuda, 1922), but no agreement has been reached on the nature of the physiological mechanism which determines these relations. Lorente de Nó (1931) is of the opinion that nystagmus and after-nystagmus are governed by prolonged central processes set in motion by brief sensory excitations in the cristæ (cf. the theoretical discussion of Rohrer and Masuda, 1926).

There are, then, four problems that confront us: (*a*) the pattern of integrated activity of the six semicircular canals; (*b*) the nature of canal tonus; (*c*) the mechanism of discrimination of opposite senses of rotation by a single semicircular canal; (*d*) the physiological basis of the time relations of nystagmus and after-nystagmus.

All these questions involve the fundamental problem of the neural mechanism of the

sensory element of the labyrinth, the hair-cell. This structure, so uniquely characteristic of the vertebrate labyrinth, has only recently been subjected to the kind of experimental study that has so enriched our knowledge of the other mechanical receptors—touch endings, pressure corpuscles and muscle spindles (cf. Adrian, 1928). In the literature of labyrinth physiology the nature of the mechanism of the sensory elements of crista and macula have remained the subject of uncontrolled speculation, which has led to great confusion. The lack of experimental knowledge is to be attributed to the extreme inaccessibility of labyrinthine end-organs, which has rendered even the surgical elimination of individual canals or otolith organs so difficult and uncertain, and which makes the task of recording electrically from individual sensory endings in the labyrinths of conventional laboratory animals almost hopeless.

In the Fishes, and in the aquatic larval forms of the Amphibia, the hair-cell is more widely distributed throughout the body than in the terrestrial vertebrates, for in addition to its typical occurrence in the various organs of the labyrinth, it is found in the so-called neuromast organs, that remarkable network of dermal canals distributed in characteristic patterns over the head and trunk, and containing at intervals along their length groups of sense organs in which the hair-cell is recognized as the specific sensory end-organ. In innervation and development this lateral-line canal system is known to be intimately related to the labyrinth, and zoologists have long recognized that the inner ear is a specialization of the acustico-lateral or neuromast system of aquatic vertebrates (Ewart and Mitchell, 1892 ; Cole, 1896, 1898).

The problem of the function of the lateral-line organs remained for long refractory to experimental study, but evidence has accumulated to show that these organs are concerned with a receptivity to vibrations of low frequency. It was at least to be expected that since the morphological identity of the hair-cells in the neuromast organs and in the labyrinth is so striking, a knowledge of the physiology of the lateral line would contribute something to our understanding of labyrinthine function. The lateral-line canals, being superficially disposed, and their nerves running for long distances under the skin, present little greater difficulty to electrical recording of sensory discharges than do the cutaneous nerves of the frog. Moreover, in elasmobranch fishes, the cartilaginous skeleton renders the labyrinth relatively accessible, and it has been possible to push the analysis of labyrinthine function to a point which, in the bony vertebrates, is probably beyond the limits of experimental possibility.

Action potentials in the lateral-line nerves of fishes were first recorded by Hoagland (1935), who discovered the remarkable fact that the neuromast organs are spontaneously active, and, in the absence of any external stimulus, discharge a persistent rhythm of impulses at low frequency. The discharge could be momentarily increased by mechanical stimuli—touch and water currents directed against the skin, and there was also evidence that vibrations of low frequency (up to 100 c.p.s.) induced a synchronization of the sensory rhythm. The interpretation of these results, however, presented difficulties, and Hoagland's assumption of two types of lateral-line receptors, rapidly adapting tactile and pressure receptors and continuously active vibration receptors, was unconvincing. The meaning of the spontaneous discharge was revealed by the work of Löwenstein and Sand (1936), who succeeded in recording from the peripheral branch of the 8th nerve supplying the horizontal semicircular canal in the dogfish, *Scyllium canicula*, and found there a spontaneous activity similar to that described by Hoagland in the organs of the lateral-line. Turntable rotation in the sense ipsilateral with respect to the semicircular canal under observation increased the volume of asynchronous afferent activity in the nerve, while *contralateral rotation inhibited the spontaneous discharge*. This surprising observation suggested that the hair-cells of the crista ampullaris, by virtue of their spontaneous rhythm of discharge, respond differentially to deformation in the two opposite directions. Deformation in one direction, corresponding to ipsilateral rotation of the canal, is signalled by an increased frequency of discharge, while deformation in the opposite direction, associated with contralateral rotation, is signalled by an inhibition of the rhythm of discharge. It was not, however, until single-fibre discharges were successfully recorded that it could be regarded as certain that this two-way mechanism was the property of one and the same receptor unit (Löwenstein and Sand, 1940*b*). That this novel mechanism is indeed characteristic of acustico-lateral receptors in general was proved by the experiments of Sand (1937), who recorded single-fibre discharges from the lateral-line nerves of *Raja*, and showed that the spontaneous frequency of discharge is increased when,

by perfusing a length of lateral-line canal, the endolymph is made to flow along the canal in one direction, and that the discharge is arrested when the flow is in the opposite direction (fig.1). Thus it became clear that the physiological properties of the hair-cell are uniquely appropriate to its peculiar morphological structure. The hair-process projects into the endolymph of a canal. Its deformation is brought about by forces imparted to

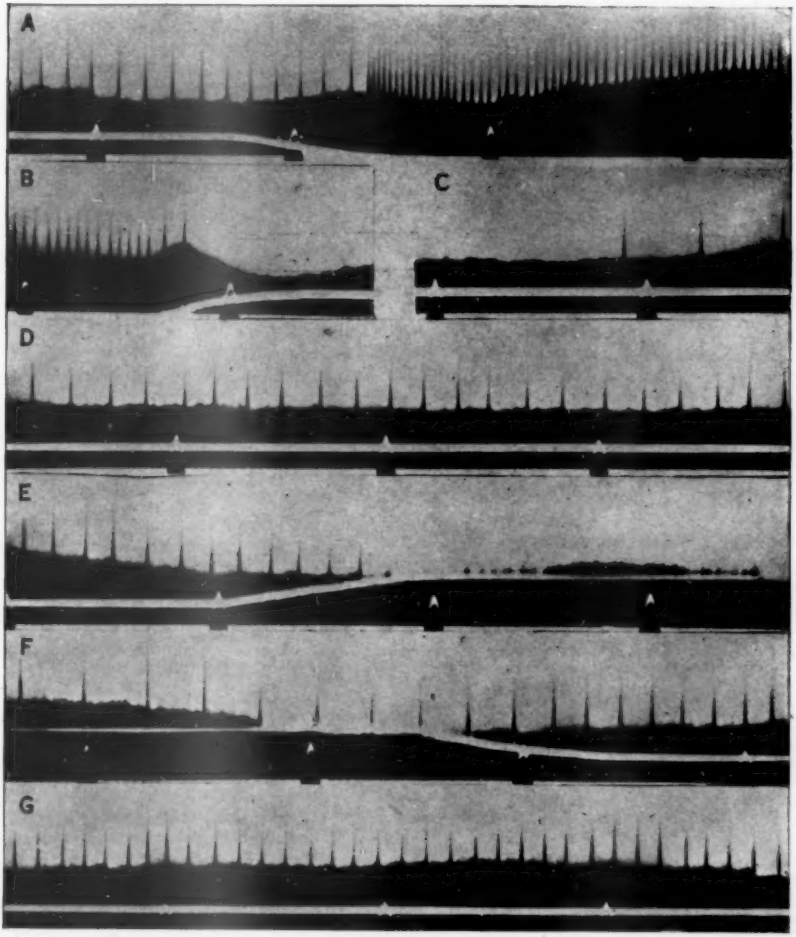


FIG. 1.—The responses of a single end-organ of the hyomandibular lateral-line canal of *Raja* to perfusion of the canal at 6 cm. water pressure. Upward displacement of white line signals tailward perfusion, downward displacement signals headward perfusion. Time signal in seconds. A, beginning of 10 sec. of headward perfusion. B, end of this perfusion. C, return of spontaneous rhythm after a silent period of 28 sec. D, the spontaneous rhythm 60 sec. after the end of the perfusion in B. E, beginning of 10 sec. of tailward perfusion. F, end of this perfusion. G, 10 sec. later, spontaneous rhythm. (From " The Mechanism of the Lateral Sense Organs of Fishes ", by A. Sand, *Proc. Roy. Soc., London, s.B.*, 1937, **123**, fig. 8. Reproduced by permission).

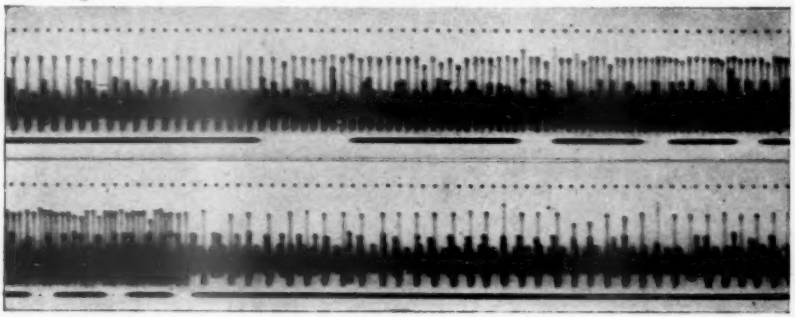
it by displacement of the endolymph, which may occur in one of two directions. The two directions of endolymph flow are discriminated by the acceleration and retardation of a spontaneous rhythm of discharge of impulses. In the lateral-line canals, which, being superficially placed, are exposed to every external mechanical influence, a displacement of endolymph is induced by touch and pressure, and by propagated vibrational disturbances. In the semicircular canals, owing to their deep situation and their specialized configuration, rotation of the canal is alone capable of causing a displacement of endolymph.

The responses of all three semicircular canals to rotation about the three primary axes have been analysed by Löwenstein and Sand (1940*a*). This was made possible by the fortunate circumstance that the *isolated* elasmobranch labyrinth makes an admirable physiological preparation, which continues to function for several hours, and in which the peripheral nerve branches supplying the three ampullæ are independently accessible. The isolated labyrinth can be mounted on a small holder which can be easily rotated in the horizontal plane and tilted about the longitudinal and transverse axes. The results of this investigation showed that, in *Raja*, the horizontal canals respond only to rotation in the horizontal plane, while the vertical canals are influenced by rotation about all three axes. For each axis of rotation the vertical canals co-operate in two antagonistic pairs, one pair being excited when the other is inhibited, but the pairs are different for each of the three axes. The anterior vertical canal is stimulated by forward tilting and inhibited by backward tilting, it is stimulated by ipsilateral sideways tilting and inhibited by contralateral sideways tilting, it is *stimulated* by *contralateral* turntable rotation and *inhibited* by *ipsilateral* turntable rotation. The posterior vertical canal is stimulated by backward tilting and inhibited by forward tilting, it is stimulated by ipsilateral sideways tilting and inhibited by contralateral sideways tilting, and (like the horizontal canal) it is stimulated by ipsilateral turntable rotation and inhibited by contralateral turntable rotation. Thus the vertical canals are all active all the time, but the pattern of their integrated activity is specific, for with each axis of rotation any given vertical canal has a different partner. During rotation about the longitudinal axis the vertical canals are laterally synergic, during rotation about the transverse axis they are transversely synergic, during rotation about the vertical axis they are diagonally synergic. The interpretation of these facts in relation to the co-ordination of labyrinthine eye reflexes is discussed by Löwenstein and Sand (1940*a*).

Records from the whole nerve branch supplying an individual semicircular canal show no more than an increase or decrease in the volume of asynchronous discharge in many fibres. They are useless for the analysis of the quantitative effects of angular acceleration and rotation at constant speed upon the activity of single receptor units. And yet these questions are fundamental to the theory of canal mechanism. According to that theory, which, in its main outlines has held its ground since it was first formulated by Mach sixty-five years ago, excitation of the crista is brought about when, during angular acceleration (or deceleration) of the labyrinth, the endolymph in the semicircular canal, owing to inertia, is displaced relative to the wall of the canal, and imparts a deformation to the sense-hairs. The converse of this proposition, namely that rotation at constant angular velocity is as much without effect on the semicircular canal as the stationary position of the labyrinth, follows inevitably from the theory. Yet there is nystagmus and after-nystagmus. And inspection of records obtained from the whole nerve branch to an ampulla when the turntable is rotated by hand does not bring conviction that excitation (or inhibition) is confined to the initial acceleration (or final deceleration). This problem has been much illuminated by the work of Steinhausen (1931, 1933, 1935), who has perfected a technique whereby the *cupula terminalis* in the living labyrinth of the pike can be observed during rotation, and its deviations compared with the reflex responses of the eyes. According to Steinhausen's observations the cupula is a jelly mass enclosing the hair processes of the crista and filling the whole cross section of the ampulla. It is an elastic body, and when deflected by a displacement of endolymph, returns slowly again to its resting position during a period of about 30 sec. Thus during and after a prolonged rotation at constant speed, deviation of the cupula occupies periods of about 30 sec. at the beginning and end of rotation, and these periods correspond with the duration of reflex eye movements.

In order to test these suppositions Löwenstein and Sand (1940*b*) recorded single-fibre discharges from the horizontal ampulla of the isolated labyrinth of *Raja* on a turntable which was driven mechanically from a falling weight mechanism which imparted an

approximately constant acceleration to the turntable. Records were taken also when the turntable was driven at constant angular *velocity* from an electric motor. The results obtained furnish a complete confirmation of Steinhausen's conclusions. During ipsilateral rotation the frequency of discharge increases *gradually* and almost linearly so long as *acceleration* continues (between 2 and 3 sec.), and the greater the value of acceleration the steeper the curve of increasing frequency of discharge. The threshold value of acceleration appears to lie in the region of 3° per sec^2. During contralateral angular acceleration the frequency of discharge decreases in a similar gradual manner if the value of acceleration is small (fig. 2). With rotation at constant angular *velocity* the picture is entirely different. The sudden acceleration at the onset of rotation results in an instantaneous maximal increase (ipsilateral rotation) or a total inhibition (contralateral rotation) of the impulse frequency, and with continued rotation at constant speed the frequency of discharge returns slowly towards its resting value in both cases. The duration of this drift in frequency back to the resting value is such that there can be little doubt that it represents



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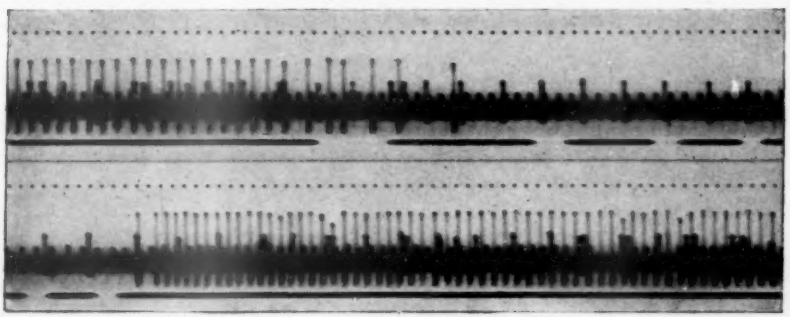

B

FIG. 2.—The responses of a single end-organ of the horizontal semicircular canal of *Raja* during turntable rotation at constant angular *acceleration*. Successive gaps in the line mark displacements of the turntable through 12°. Time in 0·05 sec. A, ipsilateral acceleration. B, contralateral acceleration. The lower strip is the continuation of the upper strip in A and B. (From " The Mechanism of the Semicircular Canal ", by O. Löwenstein and A. Sand, *Proc. Roy. Soc. London, s.B.*, 1940, **129**, fig. 3. Reproduced by permission.)

the elastic return of the cupula to its position of rest, as observed by Steinhausen. The evidence is therefore complete that the excitation of a crista, although evoked in the first instance by angular acceleration, persists for a finite period of time after the stimulating

acceleration (or deceleration) has ceased, and this duration is of the order of the duration of the elastic return of the cupula and of the duration of nystagmus and after-nystagmus found in man and other mammals (20 to 40 sec.).

We may now return to the four problems formulated at the beginning of this review and see to what extent the knowledge gained from the analysis of the activity of the lateral-line canals and semicircular canals in fishes enables us to solve them. It is a far cry from fishes to man, and it is not intended to suggest that physiological facts discovered in fishes can be applied, except with great caution, to mammals. In the physiology of the labyrinth there are great differences in the vertebrate series. Many fishes have a well-developed sense of hearing (von Frisch, 1936) but they have no cochlea and no organ of

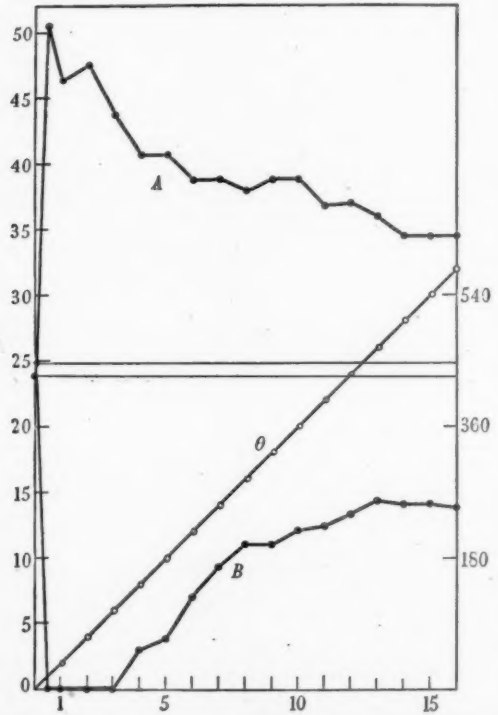

FIG. 3.—Graph of the frequency response of a single end-organ of the horizontal semicircular canal during prolonged rotation at constant angular *velocity*. θ, curve of angular displacement of the turntable, showing constancy of rotation. A, frequency response during ipsilateral rotation. B, frequency response during contralateral rotation, recorded five minutes after A. (From "The Mechanism of the Semicircular Canal", by O. Löwenstein and A. Sand, *Proc. Roy. Soc. London, s.B.*, 1940, **129**, fig. 9. Reproduced by permission.)

Corti. Their hearing is localized in the sacculus and lagæna. But the semicircular canals present a relatively constant picture throughout the vertebrate series, and it is less unlikely that their functional activity does not differ in any fundamental qualitative respect from fishes to man. The reflex responses of the eyes to labyrinth stimulation are essentially similar, though apparently different in detail, in all the vertebrates (Löwenstein, 1936).

The contribution of this work to the solution of the problems of the physiology of semicircular canals may be summarized as follows:—

(1) The activity of the horizontal canals is confined to planes near the horizontal. The vertical canals are active in all planes, and work together in antagonistic pairs, but the pairs are different and specific for each of the three primary axes of rotation.

(2) The tonic action of the semicircular canals is due to the spontaneous activity of hair-cells, which discharge a persistent rhythm of afferent impulses in the absence of external stimulation.

(3) The two-way response of an individual semicircular canal, whose discharge is increased by rotation in one direction and inhibited by rotation in the opposite direction, provides a basis for the interpretation of the persistence of reflex responses to opposite sense of rotation in animals after unilateral extirpation of the labyrinth.

(4) Excitation of the crista of the horizontal ampulla is evoked by ipsilateral acceleration and contralateral deceleration (and inhibition by contralateral acceleration and ipsilateral deceleration), but, owing to the physical properties of the cupula, the effects persist for about half a minute after acceleration or deceleration has given place to constant angular velocity or the stationary state, and thus a peripheral mechanism is provided which is adequate to account for the origin and duration of nystagmus and after-nystagmus.

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Discussion.—Mr. MAXWELL ELLIS in opening the discussion said that he supposed that most of those present were, like himself, appreciative spectators at the elucidation of one of the most difficult problems in physiology. It was now well realized that a piece of work in so-called pure physiology might at any moment be dramatically applicable in solving some clinical difficulty, and to-day the clinician appreciated his dependence upon the ingenious experimental methods of the research worker. The first point of interest in this paper was the integration of different experimental methods it embodied. Comparative anatomy provided an appropriate animal and skill in dissection a suitable preparation; observations were obtained with the technique of the radio engineer and they were interpreted by mathematical analysis applied to the specialized function of the organ under investigation. Yet the whole had been made perfectly clear to all.

He was reminded of a visit paid six years ago to Dr. W. J. McNally of Montreal who showed him the technique of exposure of the labyrinthine structures of the frog. The delicacy, rapidity and accuracy with which these operations were carried out was a surgical joy. His second point arose from the fact that Dr. McNally at that time was thinking of just such work as Dr. Sand had described and, his own technical equipment being inadequate, Dr. D. A. Ross was to assist in the radio-engineering side of the investigation. However, Dr. Ross went to Cambridge to work in Professor Adrian's laboratory and later (1936) produced a paper which dealt with the electrical activity of the frog's labyrinth. The constant activity in the nerves of the semicircular canals which is so interesting a feature of Dr. Sand's experiments was apparently not found by Ross. Both Ewald and Magnus demonstrated and discussed a form of tonus in skeletal muscle seemingly derived reflexly from the labyrinth. The constant discharge of impulses in the vestibular nerve is a complementary observation and is clearly an important finding which must be confirmed or refuted. Mr. Ellis said that he hoped Dr. Sand's work would prove the more accurate and would like to hear his further comment on the position.

His third point concerned the new account given by Dr. Sand of the functions of the vertical canals. It was not altogether surprising to hear that they react to rotation in a horizontal plane as the horizontal canals were not an original part of the vertebrate labyrinth, but it was surprising to learn that the anterior and posterior vertical canals react differently to the flow of endolymph. It was most interesting to listen to Dr. Sand's description of the coupling of these canals in movements about the three principal axes which is at variance with that of Tait and McNally. The experiments of these latter workers have also led them to consider the utricle as the synergist of the opposite vertical canals. Dr. Sand has not mentioned these structures and Mr. Ellis asked whether he had anything more to add to clarify these two diverging opinions.

Fourthly, these researches can be correlated with certain anatomical findings. Lorente de Nó showed that each crista is supplied with three different sizes of nerve fibres, and both Poljak and McNally found that the nerve enters the crista in two portions, one on the utricular and one on the canalicular side. McNally divided each in turn and found that a diminished efficiency of response occurred but that the one-sense receptivity continued. Dr. Sand now shows that there is a continuous discharge of action currents, that this discharge is increased by stimulation and diminished by inhibition. The counterpart to these reactions may perhaps be found in the three kinds of nerve-fibres and their distribution to the end-organ.

Finally, Mr. Ellis felt that everyone who was present at Dr. Dohlman's demonstration to this Section five years ago of Steinhausen's work on the cupula was pleased to see so elegant a confirmation of the theory that the elasticity of the cupula is the initiating factor in the stimulation of the end-organ.

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Mr. W. O. Lodge asked whether Dr. Sand considered that this lateral-line organ in the fish enabled it to swim straight like a torpedo. He believed he was not divulging any naval secret when he said that the torpedo was controlled by a gyroscope and always followed a sinuous course.

He had always taken the lateral line as containing a sense organ, but found a little difficulty in adjusting his ideas to these new discoveries.

Dr. Sand had mentioned the vagus nerve, and he would like to have a little guidance about the relation, if any, to the sympathetic nerve chain.

Mr. F. J. Cleminson said that he was in a special position to appreciate the work of Dr. Sand from the opportunities he had enjoyed of watching similarly delicate manipulations in the work of Mr. Hallpike and his co-workers, and he congratulated Dr. Sand on the addition he had made to our knowledge of the functions of the vestibule. This was part of the rich harvest from Adrian's single-fibre method of studying sensory responses. It was moreover most satisfactory that Steinhausen's beautiful work on the mode of action of the ampullæ had been borne out. Ewald held that the response of the external semicircular canal, for instance, was more powerful when the endolymph flow was towards than when it was away from the ampulla so that nystagmus after rotation was controlled by the left canal if the rotation had been to the right and vice versa. Had Dr. Sand found that the rate of increase or decrease in the frequency of his tonic impulses from the ampullæ agreed with this view?

The work described in this paper had carried further by an important stage the increase of knowledge of labyrinthine physiology gained during, say, the last twenty years.

Mr. F. W. WATKYN-THOMAS said that from the clinical point of view the bilateral action of the horizontal canal as described by Dr. Sand was very interesting. This was a recognized clinical fact; a labyrinth was destroyed, and from that side no reaction was obtained. That was definite for a period of usually some weeks, at the end of which time a reaction to rotation in either direction made its appearance, showing that the surviving canal must in some way or other have taken on a double function. It seemed to him, in view of the physiology of the labyrinth, that there must be some central compensation.

Dr. HUGO FREY said that Dr. Sand's contributions were of very great importance, not only because they showed the results of an elaborate technique, but because he had established certain facts which up to now were more or less hypothetical, especially the fact that there was actual discharge within the epithelial and other cells. This fitted in very well with the old theory of Ewald and with older work suggesting that there was a continuous tonus induced from the labyrinth. Ewald had spoken about a "tonus labyrinth" and meant by it a continuous and spontaneous action of the hairs of the ciliary cells. Earlier authors were, of course, not able, with the rather clumsy technique available at that time, to attempt anything like what was achieved to-day, but an experiment was made on frogs, showing that the curve of the muscular tonus in the hind leg of a frog had a special character or special line in a graph; and that there was in the living frog quite a different tonus line of the muscles of the leg as compared with the muscles of the dead frog. But if the living frog were deprived of both his labyrinths a new curve appeared in the graph which was just between the curve for the living and that for the dead frog. Consequently, the conclusion was reached that the presence or absence of an active labyrinth made some decisive difference in the tonus of the muscles, not only the muscles of the leg—the leg was only the test object—but the muscles of the whole body. The earlier worker came very near to thinking that all the symptoms which were now known as disturbances of equilibrium were really consequences of the difference in the tonus of the muscles. That theory, he thought, had long been given up, but they now had demonstrated to them the spontaneous discharge of the labyrinth which meant a spontaneous and continuous action of the sensorial apparatus, and seemed to be of great importance.

Over thirty years ago he, the speaker, had under his control a number of well-recorded deaf-mutes in a deaf-mute school, and he tried to find out whether anything could be discovered in them regarding their muscular tonus. In such deaf-mutes, in whom there was every reason to believe that their vestibular apparatus was heavily damaged or insufficient, it was shown, in a longish series of experiments, that there was pretty well-defined under-working of their muscular tonus. This, of course, was only an indirect way of finding out whether the labyrinth had anything to do with the muscular tonus.

They all knew of the antagonistic action of a galvanic current on the vestibulary apparatus, according to the direction of the current. If it ran in one way they got nystagmus in the same direction, until they changed the direction of the current, and then the nystagmus went in the opposite direction. They were accustomed to think that the galvanic current acted principally or exclusively on the vestibular nerve itself, and one was not able to understand why electric currents applied to a nerve should have a different effect when proceeding in the one direction from what they had in the other. Possibly they might have been wrong in their suppositions that the galvanic current acted exclusively on the nerve itself. It might be that this most peculiar and surprising alternative action of the galvanic current could be explained by the experiences which Dr. Sand had brought forward. Perhaps Dr. Sand could elucidate the question of the alternative action of the galvanic reaction of the labyrinth.

Dr. SAND (in reply) said that any merit for this work was equally shared by Dr. O. Löwenstein of Glasgow University and himself. Most of the publications on which this work was based were in the names of them both.

As to the first question asked by Mr. Ellis, he had little to say on the utricle. He was confident that if it had not been for the war there would have been something to say, because that was the next part of their programme; but the work was inevitably interrupted, if for no other reason than that the Admiralty took over the trawler and they could not get the material for experiments.

The work of Dr. Ross had been referred to in connexion with the apparent absence of any indication of such a spontaneous activity in the frog. He was aware that Ross failed to report effects of the kind which he and his co-worker had found, and it was undoubtedly a most important question as to how far this physiological picture was generally applicable to the vertebrates. He thought, however, that Ross had overlooked

the existence of the spontaneous discharge. When describing his preparations of the frog labyrinth, Ross noted a curious tendency to discharge impulses all the time without sufficient reason—or words to that effect. It seemed to him that there was a spontaneous discharge, but that Ross overlooked it, as one so often did in experimental work, because he had no such thing in mind. With these preparations, which inevitably involved a good deal of surgical manipulation of the delicate labyrinth, it was easy to find oneself with a preparation which was in different stages of physiological imperfection, and in which the spontaneous discharge was weak or absent.

With regard to the function of the lateral-line organs, that was still a remarkably difficult problem. It was extraordinary how hard it was in comparative physiology of sense organs to discover the function of a sense organ not represented in mammals. For example, he had been able to analyse the physiological activity of the ampullæ of Lorenzini fairly adequately, but what was their function? The same thing applied with equal force to the lateral line. The fact was undoubted and had always baffled experimenters, that one could cut all the lateral-line nerves, and the fishes, so far as their behaviour was observed—their swimming, balancing, and feeding activity—remained quite unaffected. But he must add that more recently in Professor Von Frisch's laboratory, one of his co-workers, Dykgraaf, had applied the technique of conditioned reflexes to the study of the lateral line, and on cutting the lateral-line nerves to see whether the conditioned responses did or did not persist, he found that the lateral-line system was concerned with the sort of thing about which he had been speaking, namely, delicate water currents and vibrations, mechanical stimuli of very low energy content. But one was left, nevertheless, with a rather vague picture, because one returned to the physiological findings and found that the lateral line had the properties of proprioceptor organs. Any movement of the fish's body caused discharges in the lateral-line nerves.

On the interesting question of the effect of direction of endolymph flow within the canal, and the apparent difference between the horizontal and the vertical canals, their work had confirmed what had been discovered by previous workers, that the horizontal or external canals differed from the vertical canals in that they were excited by a different direction of endolymph flow. In the horizontal canal the current towards the ampulla (ampullopetal) was the exciting stimulus, while in the vertical canals the stimulus was a current away from the ampulla (ampullofugal). The results of his co-worker and himself confirmed this, but they did not suggest an explanation. The horizontal or external canals were rather special, for they seemed to specialize in the horizontal plane of rotation. This might have a bearing on the fact that in the *Cyclostomata* there were only the four vertical canals. Thus the horizontal canals were more recent from the evolutionary point of view, and they had the property of being stimulated by the opposite direction of the endolymph flow from that which stimulated the vertical canals.

As for the two-way action of a single canal, he was interested to hear the clinical observations which had been mentioned, because they fitted in with what had been found in this work. There did not seem to him to be any other explanation than that a central accommodation occurred after the operation. The sense organ, both before and after the operation, had this discriminating response to the two directions of rotation, but in the brain, at the centre, there was a profound disorganization resulting from the operation. Instead of there being a discharge from the left and from the right which were equal when the head was stationary, there would be in the unilaterally operated animal a discharge from the intact side only, and when the head was turned to one side or the other the brain got its messages from that side only. It seemed reasonable to suppose that there was this period of time mentioned by Mr. Watkyn-Thomas during which the brain accommodates itself to the new situation.

As for the tonic labyrinth, of course, as soon as one observed this remarkable spontaneous activity, one immediately thought of Ewald and his discoveries in connexion with the tonic labyrinth. Here was the explanation of it, because if it was true that the labyrinths were sending out nervous impulses into the centre, then, when the labyrinth was removed the source of that discharge was also removed, so that it was reasonable to suppose that this was a process concerned with the maintenance of body tone.

Finally, there was the question of galvanic action. Dr. Huizinga had published a number of excellent papers on the effect of galvanic stimulation. As far as he could recollect this worker had satisfied himself that the phenomenon was to be interpreted in terms of the action of the electric current on the vestibular nerve fibres and not on the end-organ itself.

Section of Epidemiology and State Medicine

President—J. ALISON GLOVER, O.B.E., M.D.

[*May* 24, 1940]

The Clinical Teaching of Social Medicine

By N. M. GOODMAN and CHERRY MORRIS

Dr. N. M. Goodman: I do not propose to apologize for opening a discussion on a subject which may seem at first sight to be rather academic and not "actual" in the French sense of the word. First, because the teaching of medicine is the fundamental subject in the art and science which we try to practise, and secondly because the time-lag between the first discussion of a new subject for, or approach to, medical teaching and its introduction into the curriculum is often very lengthy, while the interval between the introduction of a new aspect or method of teaching into the curriculum and its effect on the main body of the medical profession must be an even longer period. For example, the swing over from environmental to personal public health commenced at the beginning of the century and yet it was only recognized officially in the syllabus for the Conjoint Examination some seven years ago. It is never too soon, therefore, to begin the discussion of any new suggestion in the sphere of medical training.

The term "social medicine" is not synonymous with public health or hygiene or preventive medicine, although it is one aspect of preventive medicine. I propose to use it in the limited sense of the social factors which affect the patient's state of health. I am not concerned with specialist post-graduate education as for the Diploma of Public Health, nor am I concerned with the present syllabus and curriculum of undergraduate education in public health and preventive medicine as a whole, except to recognize that this teaching has now emerged from the long glacial period which began with Pettenkofer and the Germans during which—to quote Professor Fitzgerald of Toronto University—"many generations of medical students were lulled to rest listening to long disquisitions on air, soil and water". This teaching has recently made important advances, which the new syllabus of the Examining Board recognized in 1933. The teaching of preventive medicine is now to some extent being linked up with the clinical teaching; thus at my own

hospital the teaching of public health and hygiene is done as far as possible by the professors and lecturers in clinical medicine. The student is coming to realize that preventive medicine is not a distinct and academic exercise taught by a strange being who only emerges once a year from some unknown place of hibernation.

The picture which the student or doctor receives of the cases in out-patients or hospital beds and even in his surgery or in the patient's home is incomplete in that it does not necessarily show the social factors which are affecting the patient. In many cases this does not matter, but in some it may lead to errors in diagnosis, in prognosis and, above all, in treatment. How can this complete picture be obtained? As long ago as 1905, Dr. Richard Cabot in Boston began to use a new auxiliary in his teaching, namely, medical social service and its personnel. I do not wish to enter the debatable land of the nomenclature of this personnel which may be, in different countries, the social worker or "assistante sociale", the almoner, or the health visitor—"infirmière visiteuse"; it is sufficient to say that in this country the almoner is probably the "person of election" for the task. Dr. Cabot set himself to study, through his social assistants, what, if any, social factors contribute to the patient's illness, and he derived his inspiration from the pioneer work of Calmette of Lille who linked up the anti-tuberculosis dispensary with the home visit of a social worker. It was in the fight against tuberculosis that the physician first adopted an active or aggressive attitude instead of waiting passively until the patient attended the clinic.

Dr. Cabot's work has spread widely in America. At Yale, since 1929, a practical course has been instituted in which the student chooses a case of infectious or contagious disease, tuberculosis, venereal disease, antenatal care, dietary deficiency, rheumatism, mental hygiene, &c., and observes it clinically with the help of his clinical teacher and socially with the help of the almoner. He visits the home, interviews societies which can help the patient and draws up a report which is discussed by a combined group of clinicians and social workers. At Johns Hopkins, a similar course is taken under Professor Canby Robinson and in one year cases were presented which suggested the discussion of, among other problems, the rehabilitation of patients with cardiac disease; the effects of poverty, of bad housing and of alcoholism; hygienic and social problems of syphilis, tuberculosis, diabetes, and paralysis. Courses on the same lines are given at Vanderbilt, Syracuse, and (for psychiatric cases) at Louisville Universities. At the University of Brussels, a somewhat different method of approach is adopted by Professor René Sand, whose clinics I have attended. A patient is brought into the lecture room and a brief clinical outline of the case is given: the social history is then described by the social assistant—usually of course after the patient has been removed. Dr. Sand then gives a brief lecture on the particular aspects of social medicine illustrated by the case. At other places on the Continent, notably at the University of Nancy in the teaching of Dr. J. Parisot, the social and medical aspects are closely linked.

What does the student gain from this type of teaching? First, and most important, the knowledge that there is such a thing as a social aspect, that his task is not necessarily finished when he has given a prescription. Secondly, he becomes familiar with the organizations—State, municipal and private—which can help his patient. Thirdly, he gains an understanding of the work of an ancillary branch of his art, namely, that of the almoner. Fourthly, from the study of a particular patient he may come to take an interest in particular problems of preventive medicine such, for example, as the differential mortality of class and occupation, eugenic selection or "suburban neurosis"—so brilliantly described by Dr. Stephen Taylor—and hence he may be drawn to a general interest in preventive medicine.

What are the objections to this teaching? The first that comes to mind is the overcrowded condition of the medical curriculum and the passionate protests which the suggestion of any addition to it arouses. No substantial addition, however, is being suggested. In Dr. Sand's method of lecture-demonstration of selected cases, the course would merely be an inclusion in the present course of preventive medicine for students and would serve to link up the latter more closely with their clinical practice. In the American method not much more is involved than an extension of the "ward round" or the out-

patients' clinic to include the social aspects, if any, of the case. After all, the curriculum is as crowded in other countries as here and yet room is found for this type of teaching.

Secondly, it may be objected that the majority of students will go into general practice and that every general practitioner knows his patients' social, family and economic circumstances, and is presumably familiar with the local social organizations. After seven years of general practice, I venture to disagree. It is true that the general practitioner knows the sort of house his patient lives in, something of his family circumstances perhaps, and whether he is a private, panel or Poor Law patient, but he knows very little of the social agencies and persons which can be brought in to help his patients. In a country practice he may know of the local Lady Bountiful, of the parish nurse, of the person from whom "letters" for convalescent homes or surgical appliances may be obtained. In an urban practice—and 85% of the population lives in towns—his horizon may be limited to the local hospitals and the Relieving Officer. And yet there are booklets running to hundreds of pages giving particulars of charitable and other social organizations in London alone. This view was strengthened by my hearing recently of a proposal by a number of general practitioners in West London to engage privately a certain ex-hospital almoner, at their own expense, to deal with their patients, make the necessary inquiries, direct them to relief organizations, &c. This seems to me to be a most significant move. Lastly there may be an effective obstacle in the absence of almoners or their equivalent from the staff of the teaching hospital. This is so in my own hospital and has hitherto prevented any attempts to introduce there teaching on these lines. However, the position there is, I believe, unique among London hospitals and is due to special circumstances.

May I end, therefore, with a plea that those responsible for teaching students should consider whether the clinical teaching of social medicine might not be introduced or extended with advantage in their medical schools. I personally look forward with confidence to a time when the notes—even if negative ones—of the social assistant or almoner on the social aspects of each case will be considered a necessary adjunct in the investigation and treatment of all cases admitted to hospital.

Miss Cherry Morris: That doctors should be socially minded is of importance not only to the community as a whole, but also to the individual patient. To many doctors the social aspects of medicine are the dominant interest from youth upwards, prompting them indeed to their choice of profession. It may be suggested that even as medical students these men need no teaching, and yet are they not the very ones who would most appreciate expert instruction both in the social implications of disease and in sources of relief, instead of acquiring knowledge by a process of trial and error?

There are others who are in danger, unless the need for a wider point of view is demonstrated, of falling into a narrow specialization in which, despite the fact that they are practising clinical medicine, considerations of humanity are lost. Further valuable work may be hindered or undone by indifference to the social background and individual needs: a clever diagnosis, or an apparent cure or a skilled piece of surgery may be undermined later by the patient's return to an unsuitable life.

In the years of material plenty immediately preceding the war there have been men in every country who have gone short of food; side by side with the modern knowledge of dietetics malnutrition has been rampant, and rates of relief have been fixed without regard to the minimum standards necessary for health which have been worked out by experts. While research has shown that certain diseases such as rickets can now be eliminated, yet in certain parts of the country this disease continues to take its toll of health. Where there has been co-ordination between medical science and the life of the patient as in the treatment of tuberculosis, of orthopædic conditions, and of certain tropical diseases, real progress has been made. The infant welfare movement in which doctor, nurse, social worker and legislator have each played their part, has accelerated the dramatic fall in the infant death-rate in this country, so that the baby in a slum district is healthier than his prototype of twenty years ago.

If we turn from the question of the general good to the good of the individual patient and of the individual doctor, we see the importance of the social outlook in the relation-

ship between the two. The patient is quick to recognize the fact that a doctor, whether it be in the consulting room, in the surgery or in the crowded hospital clinic, is treating him not as a vehicle of disease but as a human being with his own rights and responsibilities. In return he is inclined to give his trust, which is an all-important factor in his cure, and to be co-operative in his efforts to carry out any treatment. He is, in other words, likely to be a more satisfactory patient than the man who feels that his circumstances have not been taken into account and that he has received orders irrespective of his peculiar needs and without any clue as to how he is to carry them out.

For the doctor himself it is surely essential both for correct diagnosis and for success in treatment that he should be quick to recognize distress of mind or estate and their interconnexion with bodily illness, and that he should have sufficient knowledge of the resources of the community to utilize them for his patient's benefit. Indeed with the difficulties and complexities of modern medicine and modern life no clinician can afford to ignore the weapon of the social services in his fight against disease.

How is this knowledge to be given to medical students? No teaching of social legislalation or of the names and functions of voluntary and statutory bodies for the relief of distress can avail much if the student has not first learned to see health in its relation to life and has not realized that poverty and unhappiness can be the cause as well as the result of illness. He has to recognize the fact that medicine is no substitute for adequate food, that the anæmic girl will be slow to recover while working in an unhealthy basement, and that the result of even the most brilliant operation can be nullified if the patient struggles back to work before he is fit.

The clinical teacher can do much to point the way, especially in a hospital where there is an almoner's department, by insisting on having any relevant social notes on cases and by treating these particulars as seriously as he would the report from the X-ray department or from the laboratories. This is already the attitude of most tuberculosis officers and psychiatrists. He can do still more by summoning the almoner whenever needed to give a social history in front of the students, or even by pointing out that in certain cases, until he has these facts, it is useless to decide on his line of treatment. The student learns from the attitude of the medical staff that the almoner's department is not a dumping ground for the case nobody else in hospital wishes to see again, but a centre of specialized knowledge which can best be used in conjunction with and as part of the actual medical treatment.

In certain hospitals in the United States, the social worker as a matter of course forms part of the teaching "ward round". It may be argued that this involves considerable expenditure of time and that the same result can be achieved for the patient by the physician or surgeon making a point of seeing the almoner after each out-patient clinic and after seeing patients in the ward. On a busy day, however, this visit may easily be crowded out and, also, it is a less vivid demonstration to students of the relevance of the social aspect to the medical.

For work in a hospital the understanding of the patients' problems and the intelligent use of the almoner is what matters most, but for panel or private practice something more is required. Although the subject is complex, it should not be impossible to ensure that medical students should be made cognizant of the various relief agencies and of what is undertaken by the State and by private charity for those in need.

A compulsory question in the final medical examinations would emphasize to students themselves the necessity for acquiring this knowledge during their training. This could probably best be imparted by demonstrations in which individual cases were discussed by the doctor and almoner to illustrate, for instance, what can be done for the blind patient in obtaining a pension or in getting specialized training for work; for the tuberculous patient in the way of arranging sanatorium treatment or providing extra nourishment, and how the patient's family can be safeguarded from infection by being boarded out in the country. Probably a handbook for medical students could be usefully compiled to supplement this teaching.

The idea has been mooted, so far without result in England though it is practised in America, of having consultant almoners for the benefit of private and panel cases and it has even been suggested that it might be advantageous for an Approved Society to pay the salary of a trained worker. Until such schemes materialize, the private practitioner can only trust to his own knowledge and to his acquaintance with the social workers in his locality whose services can be enlisted. This in fact means that in many cases a hospital patient can hope for far more comprehensive treatment than can the private patient.

Dr. Goodman's words about the "time lag" involved between the inception of an idea and its carrying out are extremely disquieting, for if medical students are to be taught social medicine the need is immediate and there is no time to be wasted. During the first weeks of the war the attitude of public bodies towards the social services was a disquieting indication of what may occur at a time of crisis. At the end of the war the question of whether or not the social services are to be sacrificed on the altar of economy may well depend on whether the medical profession regards them as something outside their province or as an essential weapon in the fight for health. That they will be needed can hardly be disputed, for the problems which will have to be faced will be acute, problems in which health, financial worries, or maladjustment are inextricably interwoven.

When almoners were first appointed at the end of last century, it was in the double capacity of administrator and medico-social worker. The Governing Boards of hospitals have been quick to recognize what almoners can do in the way of administration: they have found them useful to assess and collect patients' payments, to deal with the Road Traffic Act, with hospital contributory funds and latterly, with the lengthy and involved forms of the Emergency Medical Service, so much so indeed that the general public is apt to believe that almoners are primarily collectors of money. Unfortunately no less a body than the Ministry of Health added, however inadvertently, to this impression by issuing in December 1939 circular No. 1938A urging the appointment of almoners to the various sector hospitals in order to assess patients. There was no suggestion of the fact that their function might also be to co-operate with the medical and nursing staff to help the patients to get the best results from treatment and to relieve misery, though, on the other side, Miss Horsburgh, Parliamentary Secretary of the Ministry of Health, laid stress on these points in an address at the annual meeting of the Almoners' Institute in February 1940.

The almoners themselves, trained as social workers, make every effort to keep the two sides of the work in harmony, but unless they have support from the medical staff of hospitals, there is a danger of their being swallowed up by administrative duties, a danger likely to increase at the end of the war. This danger can be averted if medical men themselves believe and imbue their students with the belief that no hospital is complete without a trained almoner, and that her primary duties are those of medico-social work and of the care of the patient. Unless this is clearly recognized, not at some future date but now, doctors may wake up too late to the fact that almoners' work has changed and has ceased to be an ancillary service to medicine.

(After Miss Cherry Morris' paper, Dr. Goodman and Miss Morris demonstrated a case of tuberculosis, in which no less than eleven social or medico-social units or organizations were concerned.)

Discussion.—The PRESIDENT, referring to Dr. Goodman's use of the term "gap" for this absence of teaching in social medicine in the undergraduate medical training of to-day, recalled a memorable series of articles in the *Lancet* in the 'eighties entitled "Gaps in Medical Education" written by his (the President's) father, which had been one of the main factors in adding the compulsory fifth year to the curriculum. To add any more time was impracticable, and this raised the question whether the instruction in Social Medicine so wisely advocated by Dr. Goodman should be given pre- or post-graduate. The need in undergraduate days seemed all the greater because that invaluable insight into social conditions which used to be given by extern obstetric work "on the district" was no longer available in some teaching hospitals. Social Medicine was increasingly important in his own branch of work, the School Medical Service.

Dr. LEWIS G. GLOVER said it would be of inestimable value if the teaching hospitals were to arrange during the curriculum for one of their former students who had been in general practice for some years to give three or four lectures to the senior students on the business side of general practice; and in them should be included a description of the social services, which had been mentioned in this paper. He was aware that some attempt in this direction had been made, but a more formal and effective approach to the matter on the part of those responsible for the education of medical men would seem to be desirable.

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Section of Odontology

President—S. F. St. J. Steadman, L.R.C.P., M.R.C.S., D.P.H., L.D.S.E.

[*May* 27, 1940]

Variations of the Teeth of Preuss's Colobus

By Sir Frank Colyer, K.B.E., LL.D., F.R.C.S.

Preuss's Colobus (*Colobus badius preussi*) was first described by Matschei in 1900 from two skins, one imperfect, in the Berlin Museum. As far as can be ascertained no other material, with the exception of these skins, was known of this Red Colobus until a fine collection, made by Mr. F. G. Merfield, was sent to the Museum of Major P. G. Powell-Cotton at Quex Park, Birchington, East Kent. It is seldom so large a series of any species of monkey becomes available for investigation and I am grateful to Major Powell-Cotton for sending the collection to the Royal College of Surgeons' Museum and so affording me the opportunity of its leisurely examination.

The rarity of these monkeys in the opinion of Mr. Merfield is due to the fact that they "are only found upon the rocky hills" and do not come near plantations or human habitations.

The type specimen came from Barombi, Elephant Lake, S.W. Cameroons; the Quex Park specimens were collected from the mountainous district village Nkolyam, 4¼ N.; 10¼ E. on Ekam River, S.E. Yabassi, French Cameroons.

The collection contained 67 skulls, of which 15 were males and 52 females.[1] A systematic craniometrical examination of the series was kindly undertaken by Miss M. G.

[1] The majority of the specimens are deposited in the Powell-Cotton Museum, several have been added to the Odontological Collection of the Royal College of Surgeons' Museum.

Collett, and the data preserved in the Assistant Conservator's Office of the Royal College of Surgeons' Museum. The average measurements in millimetres of the males and the females are given in the following table [2]:—

	Males			Females		
	Average	Range of variation	Percentage range of variation	Average	Range of variation	Percentage range of variation
Cephalic index	69·8 (15)	61·4—77·6	26·4	73·1 (48)	62·7—77·6	23·8
Gnathic index	85·2 (15)	81·2—87·3	7·5	83·9 (47)	79·9—87·2	9·1
Palatal index	50·8 (15)	46·6—53·7	15·2	53·9 (48)	46·1—62·0	34·5
Relation of the teeth to the palate	91·9 (14)	85·0—96·5	13·5	91·3 (46)	86·6—96·6	11·5
Mandibular length	74·1 (15)	70·0—77·0	10·0	71·9 (48)	67·0—76·4	14·0

The number of males is, unfortunately, too small to warrant even approximately reliable deductions to be drawn from the figures. The difference between the palatal indexes of the males and the females is, however, noteworthy.

The shape of the arch varies considerably as shown by the skulls illustrated in the following pages.

The principal features of interest in *C. b. preussi*, as in other members of the genus,

[2] The measurements referred to in this paper have been made as follows:—

Cephalic index. $\frac{\text{Cranial breadth} \times 100.}{\text{Cranial length}}$ The breadth is the widest part across the cranial vault. The length is the distance from the inion (external occipital protuberance) to the glabella.

Gnathic index. $\frac{\text{Basion-nasion} \times 100.}{\text{Basion-prosthion}}$ The basion-prosthion length is the length from the anterior margin of the foramen magnum to the anterior edge of the bone between the maxillary first incisors. The basion-nasion is the length from the anterior margin of the foramen magnum to the suture between the nasal and the frontal bones.

Palatal index. $\frac{\text{Palatal breadth} \times 100.}{\text{Palatal length}}$ The palatal length is taken from the middle of a line joining the posterior borders of the third molars to the anterior margin of the bone between the maxillary first incisors. The palatal breadth is the distance between the internal surfaces of the first molars at the bases of the crowns above the grooves on the internal roots.

Relation of the teeth to the palate. $\frac{\text{Tooth length} \times 100.}{\text{Palatal length}}$ The tooth length is taken from the anterior surface of the canine close to the root to the posterior surface of the third molar.

Mandibular length. The mandible is placed on a flat surface. The length is taken as the distance, in a horizontal direction, from the middle of a line joining the posterior borders of the condyles to the most prominent point of the anterior portion of the bone.

Relation of mandibular length to basion-prosthion length. $\frac{\text{Mandibular length} \times 100.}{\text{Basion-prosthion length}}$

Relation of palatal length to mandibular length. $\frac{\text{Palate length} \times 100.}{\text{Mandibular length}}$

are the frequency of (1) protrusion of the mandibular incisors, and (2) variations in position of the incisors, more especially of the maxillary teeth.

In the adult monkey the maxillary and mandibular incisor teeth meet "edge-to-edge", their external surfaces being flush with one another. This relationship of the incisors was present in twenty-two of sixty-five specimens available for examination. The method adopted in a previous publication [3] has been followed of regarding as cases of inferior protrusion those in which at least half the cutting edges of the mandibular teeth project beyond the maxillary teeth. The number of specimens showing this, or a greater, degree of inferior protrusion was 26 or 40%. In the majority of the cases the mandibular teeth were not entirely free of the maxillary teeth; in two specimens only was the protrusion marked; one of these is shown in fig. 1.

FIG. 1.—*Colobus badius preussi.* (Preuss's Colobus.) Female. A specimen showing a marked degree of inferior protrusion. Cephalic index 71·9; gnathic index 86·6; palatal index 55·4; mandibular length 67·2 mm. The Powell-Cotton Museum. M.270. ×1.

In seventeen specimens the teeth were not strictly "edge-to-edge" yet the mandibular teeth did not project to a degree sufficiently to bring them into the group of inferior protrusion. The following table gives the average measurements of the female skulls with and without inferior protrusion; some few skulls in the series could not be measured owing to their condition; skulls with a very slight degree of protrusion have been omitted. The figures are as follows:—

	Cephalic index	Gnathic index	Palatal index	Relation of the teeth to the palate
Without inferior protrusion (16)	72·9	83·7	52·3	90·8
With inferior protrusion (16)	73·7	84·8	55·5	92·5

[3] "Variations and Diseases of the Teeth of Animals."

FIG. 2.—*Colobus badius preussi.* (Preuss's Colobus.) Female. A specimen showing a slight degree of irregularity in position of the incisor teeth. Cephalic index 73·3; gnathic index 83·1 ; palatal index 57·9 ; mandibular length 75·6 mm. ×1·5. Royal College of Surgeons' Museum, Odontological Collection G. 68.772.

FIG. 3.—*Colobus badius preussi.* (Preuss's Colobus.) Female. A specimen showing a medium degree of irregularity of the incisor teeth. Cephalic index 71·1 ; gnathic index 79·9 ; palatal index 56·3 ; mandibular length 74·2 mm. ×1·5. Royal College of Surgeons' Museum, Odontological Collection G. 68.778.

The figures indicate that in the skulls with inferior protrusion compared with those having a normal occlusion the cephalic and gnathic indexes are a little greater, the palates are broader and there is less room for the teeth in the palates.

The following table gives the average relative mandibular length to the basion-prosthion length and to the palate length. The basion-prosthion distance has been divided so as to indicate the lengths of its palatal and basal or post-palatal portions, the latter being formed by the basi-sphenoid and the basi-occiput.

	Mandibular length	Basion-prosthion length: Basal portion	Basion-prosthion length: Palatal portion	Basion-prosthion length: Total length	Relation of mandibular length to the basion-prosthion	Relation of palatal length to the mandibular length
Without inferior protrusion	71·9 mm.	36·7 mm.	38·7 mm.	75·4 mm.	95·4	53·8
With inferior protrusion	70·9 mm.	36·4 mm.	37·4 mm.	73·8 mm.	96·1	52·8

The figures show that specimens with inferior protrusion are on the average smaller than those with a normal occlusion. The basal portion of the basion-prosthion is only 0·3 mm. shorter in the specimens with inferior protrusion while there is a difference of 1·3 mm. in the palatal portion; in other words, the palates are shorter in the specimens showing inferior protrusion than in those with an "edge-to-edge" bite.

FIG. 4.—*Colobus badius preussi.* (Preuss's Colobus.) Female. A specimen showing a marked degree of irregularity of the incisor teeth. Cephalic index 74·5; gnathic index 86·4; palatal index 60·3; mandibular length 73·5 mm. ×1·5. Royal College of Surgeons' Museum, Odontological Collection G. 68.782.

The columns giving the relative mandibular length to the basion-prosthion length and the palatal length indicate that, in inferior protrusion specimens, the mandible in its relation to the basion-prosthion is slightly longer, and that the palate in relation to the mandible is a little shorter than in the normal occlusion specimens.

The differences, although only slight in the case of certain of the measurements, nevertheless seem to indicate that the causative factors of the inferior protrusion are to be sought in the processes of maxillary development and growth.

FIG. 5.—*Colobus badius preussi.* (Preuss's Colobus.) Female. A specimen showing marked irregularity of the incisor teeth associated with abnormality in position of the right premolars. Cephalic index 74·6; gnathic index 84·1; palatal index 56·1; mandibular length 73·1 mm. ×1·5. Royal College of Surgeons' Museum, Odontological Collection G. 68.781.

FIG. 6.—*Colobus badius preussi.* (Preuss's Colobus.) Female. A specimen showing marked projection of the first incisors associated with some degree of rotation of the teeth. Cephalic index 72·0; gnathic index 83·9; palatal index 52·8; mandibular length 74·0 mm. ×1·5. (A private collection.)

FIG. 7*a*.

FIG. 7*b*.

FIG. 7 (*a* and *b*).—*Colobus badius preussi*. (Preuss's Colobus.) Female. In the maxillæ the first incisors project slightly beyond the line of the second incisors ; the right first premolar is rotated to the extent of about three-eighths of a circle, the second premolars are also rotated slightly; in the mandible the right first premolar is placed almost transversely to the line of the arch. Cephalic index 74·9; palatal index 49·4; gnathic index 85·0 ; mandibular length 67·8 mm. ×1·5. Royal College of Surgeons' Museum, Odontological Collection G. 68.792,

To estimate the degree of variation in position of the maxillary incisors the specimens available for examination were grouped as follows :—

(i) Those with the teeth in an even curve.

(ii) Those with a small degree of irregularity as shown by projection of the first incisors just beyond the line of the second incisors, or by slight rotation of the teeth as illustrated in fig. 2.

(iii) Those with a medium degree of irregularity of which the specimen shown in fig. 3 may be taken as an example.

(iv) Those with marked irregularity as shown in figs. 4 to 6.

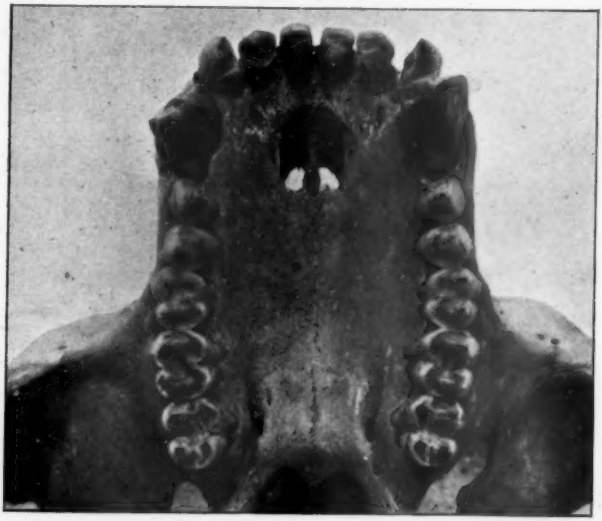

FIG. 8.—*Colobus badius preussi.* (Preuss's Colobus.) Skull of an old male. There are six teeth between the canines, four incisors and two deciduous teeth. The Powell-Cotton Museum. M.178. ×1·5.

The number of specimens in the different groups was as follows :—

	Group			
	1	2	3	4
Males (12)	1 (8·3%)	6 (50·0%)	4 (33·3%)	1 (8·3%)
Females (49)	11 (22·4%)	18 (36·7%)	12 (24·5%)	8 (16·3%)

Three male and three female skulls of the full series (67) were unsuitable for investigation. In ten cases the mandibular incisors were also irregular in position.

Rotation of the maxillary second premolar to the extent of, or beyond, one-sixteenth of a circle is a fairly common positional variation in monkeys, the internal cusp usually being directed forwards. Rotation of the maxillary first premolar is less common, the internal cusp in the majority of such cases being directed backwards. An example is shown in fig. 7, in which the right first premolar is rotated to the extent of about three-eighths of a circle, the internal cusp being directed backwards and outwards. Among 67 specimens, variations of the maxillary premolars were noted in thirty-one instances ; in two of these the rotation was marked, and in eight the mandibular second premolars were placed obliquely to the line of the arch, or were impacted slightly under the first molars.

The association of rotation of the maxillary premolars with the groups of incisors was as follows :—

Group	No. of specimens	No. with rotation of the maxillary premolars
1	12	4 (33·3%)
2	24	12 (50·0%)
3	16	10 (62·5%)
4	9	7 (77·8%)

The mandibular right second premolar in one specimen, fig. 7, was placed transversely to the line of the arch and in another mandible there was a space between the left second premolar and the first molar, the premolar being in advance of its usual position and in abnormal occlusion with the upper teeth.

Measurements of the female skulls, which are detailed in the following table, were made of the widths of the premaxillæ and of the first incisors—the second incisors were not included owing to the difficulty of obtaining satisfactory measurements.

Group	Width of the premaxillæ	Width of the first incisors	Relation of the teeth to the premaxillæ which is taken as 100
1	18·4 mm.	9·9 mm.	53·9
2	17·9 mm.	10·0 mm.	55·9
3	17·7 mm.	9·9 mm.	55·9
4	17·5 mm.	10·3 mm.	59·8

The figures show that there is a progressive decrease in the width of the premaxillæ from Group 1 to Group 4. In the last group, which includes the cases of marked irregularity, the decrease is associated with a slight increase in the width of the teeth.

It would be unwise to draw conclusions from so small a number of specimens. The inference, however, to be drawn from the measurements is that the irregularity of the incisors is associated with a decrease in the width of the premaxillæ, and that this is not associated with a corresponding relative decrease in the size of the teeth.

A most unusual abnormality is present in the skull illustrated in fig. 8. There are six teeth, all well spaced, between the canines. The outer teeth, which resemble deciduous canines, are much worn and in occlusion are in contact with the mandibular canines. The cranial sutures are obliterated but a remnant of the premaxillo-maxillary sutures persists on the left side.

Variations in number of the teeth were noted in three cases, as follows :—

(i) Absence of the maxillary second incisors. This variation was associated with absence of the fifth cusp in each mandibular third molar and with a poor development of the postero-internal cusp of each maxillary third molar. The mandibular incisors showed but little wear, but on the contrary the maxillary incisors were much worn, as if from the habit of pulling some tough material from within outwards. It is of interest to note that, although the synchondrosis between the basi-sphenoid and basi-occiput persisted, the sutures between the premaxillæ and the maxillæ were well open on their palatal aspects but closed in the lower portions of their facial aspects. The premaxillæ were small and on the left side the suture was close to the first incisor, the whole premaxillary element being poorly developed.

(ii) Absence of the left maxillary first premolar. The canine on this side had moved in a backward direction and was in contact with the second premolar and in abnormal occlusion with the mandibular teeth.[4]

(iii) Absence of the maxillary and mandibular second premolars. The skull was that of an old female, the teeth showed marked attrition. The right maxillary and the mandibular second deciduous molars were in position.[5]

The maxillary third molar in Colobus has four cusps. The outer and the inner cusps are united by two ridges, separated by a trough. The anterior and posterior margins of the occlusal surface are raised slightly so that there are shallow depressions between the transverse ridges and these margins. In one type of variation the posterior margin does not join the postero-external cusp, with the result that the depression is continued

[4] Royal College of Surgeons' Museum, Odontological Collection G. 11.7.

[5] Royal College of Surgeons' Museum, Odontological Collection G. 169.21.

on to the external aspect; the end of the ridge is raised slightly so that the external aspect presents the appearance of three cusps. In some cases the posterior border and the posterior surface are also grooved as shown in fig. 9.

FIG. 9.—*Colobus badius preussi*. (Preuss's Colobus.) Female. A specimen showing an additional cusp on each maxillary third molar. The incisors are irregular in position. Royal College of Surgeons' Museum, Odontological Collection G. ×1·5.

The mandibular third molar has five cusps. An additional cusp to the inner side of the postero-mesial cusp is a well-defined variation.

In the series of *C. b. preussi* (sixty-one) supernumerary cusps in these positions were seen in thirty-six specimens. The details are as follows:—

Maxillary and mandibular molars, 10 cases;
Maxillary molars only, 3 cases;
Mandibular molars only, 23 cases.

In one of the specimens the supernumerary cusps on the maxillary third molars were associated with two additional cusps on each mandibular third molar; in one specimen the variation of the maxillary molar was limited to the left tooth.

The following variations were also noted:—

(i) A small cusp at the middle of the posterior border of a left maxillary third molar. On the posterior border of the corresponding right tooth there were four tiny cusps.

(ii) A small cusp at the middle of the posterior border of each maxillary third molar.

(iii) A small cusp at the base of the groove on the internal surface of a left maxillary third molar. This was associated with an extra cusp on each mandibular third molar.

(iv) A small elevation at the base of the posterior border of each mandibular third molar.

An interesting abnormality of a maxillary first incisor is shown in fig. 10. Description of this tooth will be facilitated by its comparison with its opposite fellow. The internal surface of the normal tooth is shown in fig. 10 A. The outer portion is convex from side to side and the distal border is raised slightly; the inner portion is deeply concave, with a slight elevation towards the cutting edge, and the well-marked mesial border blends with the cervico-marginal ridge. The mesial portion of the internal surface of the abnormal tooth, fig. 10 B, is not so well developed as that of the right tooth; the raised border stops short of the cutting edge and there is a small kink near its junction with the cervico-marginal ridge. A groove on the external surface of the crown is continued up the root to the apex. Running up from the kink near the cervico-

marginal ridge is another groove, the portion of the root between these grooves having the appearance of an extra root fused with the main root. The deformity of the tooth would seem to be due to a dislocation of the mesial portion of the crown in a slightly backward and outward direction.

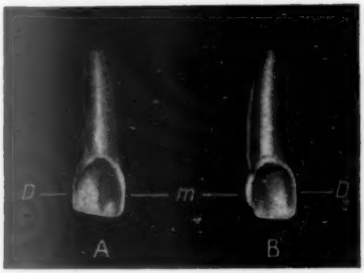

FIG. 10.—*Colobus badius preussi.* (Preuss's Colobus.) Female. Maxillary first incisors, the right tooth is deformed. Royal College of Surgeons' Museum, Odontological Collection G. 68.79. From a drawing by H. W. Norman. ×2. M, mesial surface ; D, distal surface. Part of the cutting edge of the normal tooth (A) has been worn away by attrition.

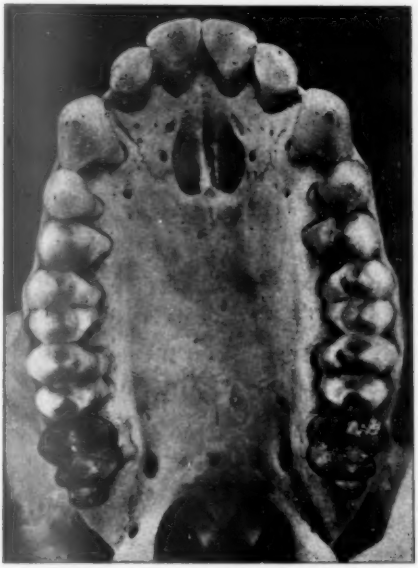

FIG. 11.—*Colobus badius preussi.* (Preuss's Colobus.) Female. A specimen showing an unusual form of wear of the maxillary third molars. The Powell-Cotton Museum. M.243. ×1·5.

One specimen showed hypoplasia of the enamel covering the lower one-third of each maxillary first incisor.

The degree of attrition of the teeth relative to the age of the animal may be regarded

as normal. The molars showed the greatest amount of wear, the loss of tissue being more marked on the inner than the outer portions of the maxillary teeth, and on the outer than the inner portions of the mandibular teeth. In the most advanced case seen the force of mastication had driven the maxillary molars outwards in an "échelon" arrangement; in another, attrition of the incisors had left a wide gap between the teeth and in another specimen the inner portions of the maxillary third molars were worn well into the dentine, the remaining teeth showing but little attrition. This specimen is shown in fig. 11.

FIG. 12.—*Colobus badius preussi.* (Preuss's Colobus.) Female. A specimen showing destruction of the alveolar bone in the region of the left maxillary molars. Royal College of Surgeons' Museum, Odontological Collection G. 169·2. ×2.

Although a generalized destruction of the alveolar bone is extremely rare in apes and monkeys in the wild state, localized areas of destruction are by no means uncommon. Early stages of the formation of pockets were seen in a few specimens of *C. b. preussi* and in two, definite spaces existed; one of these is shown in fig. 12.

[A detailed investigation of certain anatomical features of Preuss's Colobus is being undertaken by Dr. A. J. E. Cave and will be published in the near future.]

Section of the History of Medicine

President—Sir Walter Langdon-Brown, M.D.

[*April* 3, 1940]

Imḥotep

By R. J. Forbes (*Amsterdam*)

"In an old book it was recorded how King Mencheres (Mycerinos or Men-kau-ra, builder of the third and smallest pyramid of Gizeh, king of the IVth dynasty of Egypt, about 2500 B.C.) had worshipped Imuthes and had fixed his temple-ritual for ever. This old document was discovered during the reign of King Nectanebus (Nakht-ḥor-ebet, 359-342 B.C., the last Egyptian native king); but as it was written in the ancient language only the gods could understand it. But the author of this papyrus, Nechautis, had promised the god to translate it into Greek, because he had delivered his mother of a serious attack of quartan ague. But the task was difficult and the days went by as he put off its execution. Then the god struck him with illness. In the night when everyone sleeps except sick mortals, he lay in fever with pain in his side, coughing and choking while his mother watched at his bedside. Suddenly, and it was no dream, a divine and awe-inspiring figure appeared before her. The spectre was taller than any human being, it was clothed in shining garments and held a book in its left hand. It inspected Nechautis twice from the head to the feet and disappeared suddenly. As the mother recovered from the shock she woke her son and found him perspiring over his whole body, but his fever had gone. And a wonder had happened, for he had seen in his dreams what had appeared to his mother. When he worshipped the god in gratitude the priest pointed out that the god would be far more pleased if he took up the long-postponed translation than by the offerings which he had brought to the temple. And so Nechautis ardently attacked his task and translated the book of the wondrous deeds of the god Imuthes. Now every Greek tongue can recount the story of Imuthes and every Greek will praise him for ever."

This is a summary of a second century papyrus [6] which is certainly meant to advertise the temple and oracle of Imuthes at Memphis, where the Greeks worshipped him under the name of Asclepios. Only the introduction of this papyrus has been recovered, but it hardly differs from the many wonders, stories, miracles and cures by dreams published to advertise many Asclepios temples in Greece, describing in detail cases of many patients in order to attract new ones [8].

This god—Asclepios, Imuthes or Imouth—is mentioned in many theological and philosophical books of the first centuries A.D., especially in the so-called Hermetic books. These were typical products of Hellenistic syncreticism, combining ancient lore and legends of the East with the younger philosophical systems of the Greeks. In these melting-pots of quaint theories the old gods are mentioned under names of Greek gods and voice opinions which have nothing to do with their original roles in the Egyptian pantheon.

In these books Imouthes-Asclepios is first of all *god of medicine*. In the Hermetic work *Asclepios* he is called "god who keeps mankind alive", "he who gives life to the supplicant", "he who gives life to whomsoever obeys him", "he who looks after the sick", "he who gives a son to whomsoever has none". In *The Virgin of the World* (another Hermetic treatise, fragments of which have survived) he is called "Asclepios, the son of Hephaistos" and "king of medicine", but he is also "king of poetry". He is "god by the grace of Ptah who is Hephaistos". Another of his names is "Asclepios, the bald Imouthes, councillor of Hephaistos". A third Hermetic book mentions "he who comes

if we call, who bans disease and who heals the body". This is but a small selection from the many references to Imuthes in the Hermetic books.[1]

As a *wise old man* he is depicted in a dialogue between Hermes and Asclepios, while he has some renown as an astrologer. Vettius Valens (second century A.D.[2]) mentions a book called *Astrologumena* which is said to date from 150 B.C. and embodies many observations from Imouthes.

As an *alchemist* of repute he is quoted by Zosimos (third century A.D.) who calls one of his alchemical books *Book of Imouth on What Can Be Achieved by the Hand.*

His worship continued up to the fifth century A.D.[3], not only in his chief temple in Memphis but also in Thebes and even in the island of Philae in the far south.

Except in a few late temple reliefs he is always depicted as a man. Bronzes of Imouthes portray him as a sitting, bald man, clothed in a long tight robe, who is holding the ends of an opened papyrus roll in his hands and seems to be reading in it. Except in a few cases[4] all these bronzes depict him sitting. They are fairly common in the museums of Berlin, Hildesheim, Cairo, &c. [13]. Only on very late temple walls do we see him with divine attributes like the other Egyptian gods. Therefore, although Hellenistic Egypt recognizes him as the Divine Son of Hephaistos (the Greek name for the old Egyptian god Ptaḥ), the Egyptians always realized that behind this figure of the god there was a man who had lived many centuries ago. Even in the third century A.D. a Christian writer such as Clement of Alexandria mentions the deification of "Asclepios of Memphis".

When did this deified man live and what details do we know about his life? These questions were answered by Sethe [15] in one of his brilliant essays, but his details were further supplemented by Hurry [9] while Egyptian archæology has discovered valuable evidence in the last fifteen years. Thus it is certain that Imḥotep was an historic person of great importance in ancient Egypt. The earliest proofs of a god Imouth-Asclepios date from the Safte (663-525 B.C.) and late periods in Egyptian history covering the last efforts of a waning Egyptian culture until the Ptolemaic dynasty imposed a lasting foreign dominion. Not a single statuette dates from an earlier period than 700-332 B.C. The earliest priest of the god Imouthes in his temple at Memphis lived in the reign of King Amasis (570-525 B.C.) and he is at the same time priest of the cult of the ancient king Djozer. This combination of priestly functions is an important clue, as we shall see.

Imḥotep's cult cannot have been of much importance in the sixth century B.C. and was only of the common type of cult of a dead person. Herodotus, when visiting Memphis, observes (II.50): "The Egyptians differ from the Greeks in not paying divine honours to heroes of the past." Imḥotep's cult was therefore not of great importance at the date of this visit in 460 or 448 B.C.[5]

There is ample evidence that the Egyptians knew that Imḥotep was a living person who held a position of importance at the court of a king long dead, King Djozer (IIIrd dynasty, about 2775 B.C.). This is what the priest, Manetho, speaks in his History of Egypt written in the third century B.C.: "Tosothros (Djozer) during whose reign Imuthes (Imḥotep) lived who was the Asclepios of the Egyptians because of his relation to medicine. He also invented the building in stone and occupied himself in writing." It is true that in late Roman times the Egyptians gave him divine attributes and titles such as "ntr-mnḥ", that is "merciful god", but in the early stages of his deification all his titles are human ones and, therefore, they are put before his name in books and documents as was the custom among the Egyptians. Only in the case of gods do the titles follow the name, never in the case of human beings. This also proves that both the wife and mother mentioned in the texts were human too. Even after deification he retains such human titles as

[1] The reader will easily multiply these references from the standard edition of the Hermetic Corpus (W. Scott's *Hermetica,* 4 vols., Oxford, 1924-36) or from Ménard's French edition of the principal treatises [12]. The translation by Mead [11] is not always dependable, but will also demonstrate the frequent references to Asclepios-Imouth in this Corpus.

[2] Vettius Valens, *Ἀνθολογίων libri primi fragmentum* ed. G. Kroll, Berlin, 1908. *See also* F. W. Boll, *Erforschung der antiken Astrologie,* Leipzig, 1908, p. 106; Boll-Bezold, *Sternglaube und Sterndeutung,* Berlin, 1926, p. 24.

[3] Ammian. Marcel. XXII, 14, 7; Vita Hilarü 21.

[4] Berlin No. 2518 and a small statue in the Liverpool collection.

[5] For these dates see Powell, *History of Herodotus,* London, 1939, p. 29.

" Inspector of the Buildings of Upper and Lower Egypt ", " Inspector of the (pyramid-) Town ", " Vizier ", Chief Ritualist of the King of Upper and Lower Egypt ", " Chief Scribe of the Grain of the King of Upper and Lower Egypt, Djozer ", " Ibis " (sage), " Scribe of the Books of the Gods ".

The main part of the cult of Imḥotep consisted of the recital of texts from the *Book of the Dead*, &c. This cult is definitely connected with " the place where thy body is buried ", that is with the temple-grave of Djozer, his pyramid at Saqqarah and the burial ground of the sacred Apis bulls, all near Memphis. Even a late Hermetic book like the *Asclepios* still mentions this " temple near Crocodilopolis (Memphis) where his body lay while the better part soared to Heaven where he still helps everyone in need, whom he formerly assisted with his knowledge of medicine ". One of his titles is that of an architect ; he is called " he who draws the outline of the temple for the gods ", because the planning of the temple of Edfû was ascribed to him. These plans were found, according to the legend, in a book " which came from Heaven " somewhere to the north of Memphis, again in the neighbourhood of King Djozer's temple and Pyramids. The title " Scribe of the Books of the Gods " is a very ancient one, pointing to Djozer's period, i.e. the Old Kingdom, the earliest phase in Egyptian history (before 2000 B.C.), and so are the titles " Chief Ritualist " and " Vizier " or " Chancellor ". All the evidence indicates that the deification followed, in the last period of Egyptian history, a cult of more than 2,000 years' standing of the deceased Imḥotep, in which he was honoured with his king, Djozer, as one of the greatest figures of the past. This late period which tried to find new strength in the earliest period, the youth of Egypt, had a strong tendency to venerate any important person from these early days. It was also believed that his mother was a human being but that his father was the god Ptaḥ, though the name of his father, Ka-nofer, is mentioned in one text. It is, however, a general characteristic of the heroes of classical and even pre-classical antiquity that they had a heavenly father and a human mother.

After his deification Imḥotep was combined with the god Ptaḥ, his alleged father, and the lion-headed war-goddess, Sechmet, in a triad, an arrangement of three gods much favoured by Egyptian theological speculation. The choice of Ptaḥ as the divine father of Imḥotep is very important, for Ptaḥ belongs to the oldest and most important group of gods of the Egyptian pantheon. He rose to eminence very early as the god of Memphis, the capital of the Old Kingdom dynasties. This god is always represented as an idol in the form of a mummy, never as a divine human being nor a god in human form but always as a statue of a god. He is perhaps the most impersonal and irrational god of Egypt : a philosophical conception who was addressed as " Father of the Gods ", " Father and Mother of the Sun-god ", " Mouth that named everything ". He is the head of a very old system of deities which struggled for supremacy with the system connected with the Sun-god of Heliopolis, Ra, even in prehistoric times [14]. As the wise creator-god, he is the patron of artists and craftsmen, especially of goldsmiths. In the shadow of this important god, the architect and vizier, Imḥotep, became the god of medicine and science. His statues adopted the human-mummy type of those of his father, Ptaḥ.

Imouth or Imouthes is the Greek form of the Egyptian name Imḥotep (more correctly spelt " Ij-m-ḥtp ", meaning " he who comes in peace "). This name, as well as those of his wife and father, are fairly common Old Kingdom constructions. This again points to a historical figure from King Djozer's period who, like his fellow-architect, Amenḥotep, son of Ḥapu (who lived during the reign of King Amenḥotep III, about 1400 B.C.), was deified long after his death.

After the deification of Imḥotep, an architect of King Darius (495-491 B.C.) wrote his own genealogy on the rocks of Wadi Hammamat, tracing his line back to Imḥotep and his father, the architect Ka-nofer. This genealogy may have been invented for the glory of the writer, but it proves, with so many other instances, that Imḥotep had been revered, in the period between his death and deification, as a sage of the heroic age of the pyramids, as are a few others whose books and sayings are quoted in many texts.

Thus, the " Song of the Harp-player of King Intef " (XIth dynasty, about 2000 B.C.) is a lament on the transcience of all earthly values. It points out that the temples and graves of kings and prominent men have been destroyed, but that the words of wise men like Imḥotep and Hardedef (son of King Cheops) are on everybody's lips. Another old legend tells us how King Djozer consulted the wise Imḥotep after a terrible drought had starved all Egypt because the Nile had not overflowed its banks for seven years. After consulting the books of the gods in the temple, Imḥotep hastened back to tell the king about the

springs of the Nile at Elephantine where the god Chnum reigned, and the king, feeling that he had neglected the god, made him a magnificent present. He dedicated to the god a piece of land along the river banks, twelve miles of land on each side, the so-called Dodekaschoinos, with the river-tolls, a valuable possession that belonged to the Philae temples later on. This story, the original of which must be of Old Kingdom date because of the ancient philological forms in the text, refers to Ptah as the father of Imḥotep and gives the latter titles such as "Scribe" and "King's Councillor". Even during the Middle Kingdom the scribes must have venerated Imḥotep, for they offer him a libation before dipping their brushes in the ink.[6]

More light was shed on the historical Imḥotep by the splendid excavations and archæological studies at Saqqarah by Quibell, Firth, Gunn and Lauer who investigated the surroundings of the Step-pyramid. This proved to be the tomb not only of King Djozer but also of two of his daughters. The pyramid, encased in slabs of shining white limestone, was surrounded by a wall which also enclosed a complex of temples and pillared corridors, the first series of buildings in which natural hewn stone was used as a building material. Of course, during the first two dynasties and even in prehistoric times the Egyptians had worked stone and produced those beautiful alabaster vases which are the pride of many museums, but their buildings were constructed of wood, reeds and sun-dried bricks formed from "sebach", the mud from the Nile. This is apparent from the forms used in Saqqarah. Sometimes floors had been made of stones, or even rooms were encased with stone slabs, but in Saqqarah the old unstable, temporary materials were replaced by stone. Here for the first time the ancient Egyptians built truly "for eternity".

Thus, the archæologist proved the truth of the tradition that Djozer and his vizier, Imḥotep, were the first to build in stone. The proof that Imḥotep was the architect of the Saqqarah complex was found in an inscription on the base of a statue discovered in the 1925-26 season [7]. It reads: "Chancellor of the King of Lower Egypt, First under the King of Upper Egypt, Administrator of the Great Mansion, Hereditary Noble, High Priest of Heliopolis, Imḥotep". Although the greater part of the statue is lost, we can reconstruct it fairly well from the fragments and observe that it was a statue of the king offered to him by his vizier. The titles carried more weight during the Old Kingdom; later in Egyptian history they became rather common possessions of many persons at the king's court.

There is also a fortress built by King Djozer in the Delta and bearing the name "Gate of Imḥotep". We may thus infer with considerable certainty that Imḥotep was in fact the master-mind behind these magnificent structures. And, indeed, these buildings show great constructive skill, but it is not the skill which comes from centuries of experience in the handling of stone and the realization of the possibilities inherent in that material. Everything is built up solid and then carved like a statue. The vertical grooves or panels in the walls have been laboriously cut out after erection, with flint borers and copper chisels as the Pyramid Age knew no bronze. There is great waste of labour and material in the dressing and fitting of small blocks of stone. It is the art of stone-cutters who had a long tradition of stone vase-making, an industry which had just begun to decline in the IIIrd dynasty, but who were treating the stone almost as a plastic material. Just as the makers of stone vessels sought to beautify and make more permanent the forms of clay vessels, while creating new forms for themselves, so did the first builders in stone seek to render imperishable the forms of mud-brick and reed building.

The veneration paid to Imḥotep is due to the tradition (proved to be correct) that he was the first great genius who made a tremendous step forward in the arts. He had seen mud-brick tombs decay in sun and rain and turned them into stone that they might last for ever. He was not yet aware of the limitations and possibilities of this new material and used small blocks of stone, in spite of waste of labour, because his workmen could handle them easily and the resulting narrow courses would have the appearance of the old-fashioned brickwork. The use and handling of large blocks of stone were mastered by the pyramid-builders of the IVth dynasty. The import of timber from Syria started in the reign of the first king of that dynasty, Sneferu, and enabled the Egyptians to make more efficient use of man-power for moving weights, by means of sledges, rollers, levers, and rafts and tracks of wooden baulks. Only then could the natural possibilities of stone be fully exploited.

[6] Aeg. z. XXXVI, 1898, 147 and XL, 1902, 146.

Of course the limitations of IIIrd dynasty architecture do not diminish our respect for Imḥotep, the first man to build in stone. He may not have been the personal inventor of the art of building in stone—if, indeed, such a person ever existed—but he was the first man to experiment with a new technique [16].

The titles mentioned on the base of the statue again show that we know of no direct connexion between Imḥotep and medical science. But tradition insists on the role played by Imḥotep in the history of medicine and there may be some plausible reason for this belief.

Egyptian medicine was very important in the pyramid age. This is shown by the traces of operations which we find on mummies and remains of skeletons, but we have also reason to believe that many later medical papyri are based on Old Kingdom originals. Thus the famous Edwin Smith Papyrus [1], which probably bore the title "Secret Book of the Physician", is based on an original of this period; this conclusion is reached from the archaic philological constructions found. Then again, in the Vth dynasty inscriptions we meet with many references to medical books and to specialists. A specialist in diseases of the eye, stomach, &c., named Irj,[7] is mentioned in one such text.

The highly-developed state of Egyptian medicine in the pyramid age was well known in tradition and the combination of names like those of Imḥotep and other wise men of the pyramid age with this medical tradition in later periods seems quite logical when we consider that many of the historical details now made available to us by archæological research were then unknown.

Modern speculation has even tried to shower praise on Imḥotep as the inventor of the Sothic cycle and the improvement of the Egyptian calendar, but these suggestions of Breasted [2] appear to be without foundation.

Our general conclusion from the known facts is, therefore, that Imḥotep, vizier of King Djozer, was the first person to execute large stone buildings, such as the Step-pyramid of Saqqarah and the surrounding temple-complex. After his death his memory was venerated by many generations; the cult of the deceased Imḥotep never died out. Tradition clothed this veneration with many legends of a wise man, skilled in the arts and in medicine, and he was finally deified in the last period of Egyptian history when the traditions of its youth were especially resuscitated. The first architect and builder in stone thus became the god of medicine and science, although he had only remote contact—if any—with medicine.

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[Dr. Forbes is resident in Holland which has been occupied by the Germans since his MS. was received. It has therefore been impossible to submit to him any proofs of his article.]

[7] Junker, *Z. f. Aeg. Sprache*, 1927, **63**, 53.

Engraved Portrait of a Centenarian

PUBLISHED IN 1806

By Sir StClair Thomson, M.D.

This engraving, which I am offering to the Society, is of both artistic and medical interest. There is evidence that the subject of it had passed her 100th year ; it represents a vigorous personality, yet with well-marked osteo-arthritis of her hands ; the quality of the engraving is delicate, and I believe the print is a rare one. The *Catalogue of Engraved British Portraits* preserved in the Department of Prints and Drawings in the British Museum (Vol. I, page 32) refers to two prints of this same old lady. The first one is catalogued as : " Centenarian, born 1702. Aged 104, whole length to right, seated. Etching and aquatint $10\frac{7}{8} \times 8\frac{1}{8}$. Artist unknown ; engraved by D.M.F."

The second print in the Museum is catalogued as : " Aged 106, whole length to left ; seated by table on which is a ' Plan of Oxfordshire '. Published by W. Richardson, 1809. Line engraving $9 \times 5\frac{3}{4}$ inches. Artist unknown ; Engraver Anonymous."

The print which I exhibit is somewhat different and comes between these two dates. Like the first print in the British Museum, it is noticed that in the top left-hand corner there are the initials of the engraver, D.M.F. It bears the following inscription:

" To the President and Fellows of the Society of Antiquaries and to all other Lovers of the Antique, Elizabeth Alexander, widow, aged 104, humbly dedicates this portrait of herself. Price 5/

Pray remember the Poor."

Below, the margin states :

" Published as the Act directs, May 8, 1806, for Elizabeth Alexander and Elizth Atkins No. 11 Hanway Yard."

We are therefore looking at the portrait of a lady in her 104th year, who lived at least another two years. I trust there was sufficient response to her appeal for the purchase of these very good prints to make her last years comfortable, in spite of her arthritis. Her virile look shows she had the personality which conduces to and is often associated with old age.

Two Engravings (Dated 1802) of the Drinking and Dipping Wells in Hyde Park

By Sir StClair Thomson, M.D.

One print is labelled " The Drinking Well in Hyde Park : Le Puits à Boire à Hyde Park ". It was engraved by James Godby from a painting by Maria Spilsbury. It bears the date 1802 and depicts, in the charming costume of the period, a lady paying for glasses of water which are being handed out to her children. She is accompanied by a little King Charles' spaniel, and a negro servant carries her umbrella.

The other engraving is labelled, " The Dipping Well in Hyde Park : Le Puits à Baigner à Hyde Park ". The engraving is by James Godby from a painting by F. Wheatley, so well known for his " Cries of London ". This print also bears the date of 1802, and shows a group of ladies with their nurses, and accompanied by a male parent, bathing some children in a very primitive bath. There are deer wandering in the background.

These two particular engravings are more of historical interest than artistic value. Still, the fact that the titles were printed in French as well as English shows the vogue which existed abroad more than a century ago for English engravings. This vogue still exists, for I know that two beautiful colour engravings, of these two subjects, were recently bought at Sotheby's, to be disposed of in Paris, for over sixty guineas. At the present moment I know of a pair of these colour prints for which the owner is prepared to accept £80. Until some other Fellow comes forward to present the Society with prints of such fine quality, I hope it will accept as a curiosity the two tinted engravings which I now offer.

Readers of that erudite and charming book entitled *Old London's Spas, Baths and Wells*, by Dr. Septimus Sunderland, will find in Chapter V (p. 52) a description of St. Agnes' Well which existed as late as 1804 in Hyde Park near the head of what is now the Serpentine

and on its eastern bank. He reports that there were two springs. One was used for the immersing of children, and was known as the "Dipping Well". The other, the "Drinking Well", was said to be medicinally potent, and was sold in glasses by an attendant to visitors, amongst whom were many children of the richer classes. The water was probably mildly chalybeate.

The Serpentine was not, in those days, the spacious and ornamental lake we now know. We gather, from a learned communication on *West London Rivers* by the late Dr. Clippingdale,[1] that at the beginning of last century this part of Hyde Park was occupied by a series of ponds of dirty and stagnant water, supplied by a river known as the "Westbourne", which arose in the high ground of Hampstead and, after being joined by the "Cool Bourne" (Kilburn) and a tributary called the "Tyburn Stream" entered Hyde Park. On emerging from the south side of the Park, the "Westbourne" passes under Knightsbridge and finally enters the Thames near Chelsea Hospital. But, up to the early part of last century, the "Westbourne" had not, during its passage through Hyde Park, been banked into the ornamental lake we know to-day as the Serpentine. The river wandered about in a series of ponds. It cost Parliament £28,000 to alter this. Later on, in 1834, the rapidly increasing suburb of Bayswater discharged so much sewage into the Serpentine, that it was disconnected from its parent stream, the "Westbourne", which was then converted into a drain.

The Serpentine is, at the present time, supplied with water from three sources, (1) surface water, (2) from the round pond, and (3) from a well called "St. Agnes' Well". This well can to-day be located at the northern end of the Serpentine, close to Jenner's statue. Dr. Septimus Sunderland has very kindly supplied me with a recent Ordnance map of Hyde Park (dated 1906) where the location of St. Agnes' Well is marked, just north of the Jenner statue.

This use of the wells has now, fortunately, ceased, nor does the Serpentine any longer serve, as it did in the days of Queen Anne, for drowning illegitimate babies!

Still, as we all know, history repeats itself, and these prints show that the "paddle pools" which were recently arranged for in Hyde Park (when the late George Lansbury was Commissioner of Works) were anticipated by the Dipping and Drinking Wells one hundred and thirty-eight years ago.

[Sir StClair Thomson has kindly presented these three engravings to the Royal Society of Medicine. They are now in storage for the duration of the war, but in normal times may be seen in Room 23 at the Society's house.]

Dr. Richard Mead's Harveian Oration

By Sir Walter Langdon-Brown, M.D.

Richard Mead is so well known that I need say little concerning his life. Like many a man of light and learning he was a son of the manse. He first studied classics and philosophy at Utrecht, but four years later, in 1692, he went to Leyden for a medical training. Here the famous Boerhaave was a fellow student, with whom he kept up friendship all his life. He subsequently graduated at Padua. In 1702 Richard Mead's book on the action of poisons attracted so much attention that he was elected Fellow of the Royal Society the following year, in which year he also became Physician to St. Thomas's Hospital. For some unknown reason he did not apply for admission to the Royal College of Physicians till 1708, becoming a Fellow in 1716. He held most of the important offices in the College but declined the Presidency. He had a practice that was both fashionable and lucrative, and during the height of his fame resided in a fine mansion in Great Ormond Street which afterwards became the Hospital for Sick Children. Here he entertained lavishly. He was a great collector of statues, coins, gems, prints, drawings and rare books. I have here the catalogue of the sale of his collection which was very kindly given me by Dr. Parkes Weber. It runs to 246 pages, and the sale lasted for weeks. However, so moderate were the prices then prevailing that the whole collection of really valuable things only realized something over £16,000. Like Radcliffe he made a magni-

[1] Clippingdale, S. D., West London Rivers, extant and extinct, *West London Medical Journal*, 1909, **14**, 1.

ficent use of his fortune in the encouragement of art and science and in charity. It is not surprising, therefore, that he did not leave a large fortune, having spent so much on his own enjoyment and that of others. Samuel Johnson said of him that no man of his time enjoyed more of the broad sunshine of life. It was he who persuaded Guy to use his wealth to found the hospital to which for more than a century Mead's own hospital was a close neighbour.

He delivered the Harveian Oration in 1723 under the Presidency of Sir Hans Sloane, this being the thirtieth occasion on which it was delivered. I have here a finely printed copy of the Oration, which is in Latin—as indeed they always were until 1864. It should be remembered that although this Oration is now generally devoted to a laudation of some aspect of Harvey's work, it was not originally intended for such a purpose, for Harvey himself established it in his lifetime for the commemoration of benefactors, to be accompanied by an exhortation "to search and study out the secrets of Nature by way of experiment and also for the honour of the profession to continue in mutual love and affection". Mead's oration was brief and consisted of a simple recapitulation of salient points in the history of Greek and Roman medicine, with a passing reference to the mediæval schools of medicine, and then mention is made of various benefactors. It would be considered inadequate as an Oration to-day and contrasts in this respect with Walter Charleton's oration of 1680, which Sir Thomas Browne considered good but too long—it was about 7,700 words; and although indeed he would not be considered a concise writer himself, he wrote an oration in about 2,500 words to show his son, Dr. Edward Browne, how it should be done. Unfortunately for his paternal pride, Dr. Edward Browne was never invited to give the Harveian Oration, and Sir Thomas died before his son reached the still greater distinction of the Presidential Chair.

It is therefore not mainly on account of the Oration itself that I am showing this book. It is because of the interesting Dissertation which is attached to it—for this deals with certain coins, not merely medals, struck at Smyrna, which he claimed were in honour of physicians. This interpretation evidently became a matter of controversy, and with the aid of Dr. Parkes Weber's encyclopædic knowledge I have come to the conclusion that although the figures of Apollo, Æsculapius and Hygeia repeatedly appear on the coins, they were more probably struck during the term of office of certain magistrates and high priests. It may be noted that the names of the physicians to whom Mead attributes them do not appear on the coins, and it is unlikely that the status of physicians was such that actual coins used as currency would be struck in their honour. At any rate such coins are not described in Barclay Head's monumental work.

This particular copy of the Oration is of special interest as it belonged to Thomas Hollis, F.R.S. and F.S.A. of Lincoln's Inn who was well known as an ardent republican, so much so that he could not abstain from endorsing the fly-sheet with a reference to the Revolution of 1688 which he stated restored liberty to the Constitution, while on the title page he has written a caustic quotation from John Milton in which he grades politicians below libertines. At the end of Mead's dissertation Hollis gives references which I take are to some literature on the controversy concerning the attribution of these coins to physicians. The copy has a further personal interest as it is lent me by a descendant of William Harvey.

Section of Ophthalmology

President—MALCOLM HEPBURN, F.R.C.S.

[*June* 14, 1940]

Cataract in Adult Rickets (Osteomalacia)

By J. PRESTON MAXWELL, M.D., F.R.C.S., F.R.C.O.G., and H. T. PI, M.D.

(From the Departments of Obstetrics and Gynecology and Ophthalmology, Peiping Union Medical College)

AT the time of our paper on Adult Rickets delivered to the Royal Society of Medicine in 1934, we were already aware of certain degenerative processes which are occasionally seen in connexion with osteomalacia. One of us (Pi, 1934) took up the study of cataract in relation to our osteomalacia cases, and in relation to what goes by the name of "Cataracta tetanica". Cataract has never been specially associated with osteomalacia, which makes the subject an important one, as it is clear that the term "cataracta tetanica" is, in some cases at least, a misnomer.

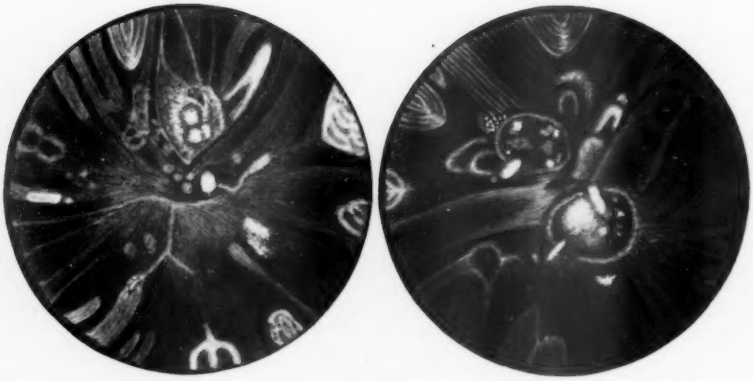
One has to specially look for this form of cataract, as the subjective ocular symptoms are slight; and as the majority of our patients are illiterate, it is only when the disease has considerably advanced that the patients are likely to complain of loss of vision.

What is the incidence of the trouble in osteomalacia cases?

Out of 60 well-marked cases Pi found 13 cases of this form of cataract, making an incidence of 21·6%.

The numbers are of course small, but the probable incidence in marked cases is at least 15%.

Cataracta tetanica was first described in 1872 by Logetschnikow. He reported 14 cases in which spasms were present at the time of examination or a history of convulsions preceding the disturbance of vision was obtained. The same trouble was also observed by Schmidt-Rimpler (1883); Bernhardt (1891); Wettendorfer (1897), and others. These cataract cases were mostly in young or middle-aged women, none of whom was stated to have been suffering from osteomalacia, though it is quite possible that some were so suffering. Bernhardt's observation first led him to use the term "Cataracta in idiopathic tetany" for the kind of cataract in which the nature of the tetany was not known.



Right eye. Left eye.

FIG. 1.—Front view of slit-lamp pictures of Case 2 (see Table p. 30), drawn in April 1933.

Right eye. Left eye.

FIG. 2.—Front view of slit-lamp pictures of Case 2, drawn in November 1933.

Landsberg (1888) later recognized and reported cataracts in post-operative tetany, i.e. the cataracts developed after accidental removal of the parathyroids or were due to their degeneration after thyroidectomy. Erdheim (1906) and others have also described these in experimental work. Cole (1930) in giving an account of a typical human case, cites descriptions of cases by Jacques, Saintor and Peron, Aub and Hunter.

So it is clear that the disease can be classified into cataract in post-operative cases, and cataract in idiopathic tetany. According to present knowledge both of them are associated with disturbance of endocrine secretion, the only difference between them being that the development of cataract in the former has a known cause, i.e. it results from the removal of the parathyroid glands, while the ætiology of the latter has not yet been clearly explained. Similar symptoms such as changes of hair and finger nails, caries of teeth, and diminished activity of bone growth, have been observed in both kinds of affections. Tetany is common in osteomalacia, and where a history of tetany cannot be obtained there has often been numbness of hands and feet.

A review of the literature reveals that the cataracts in association with idiopathic tetany are reported as follows: (1) Lenticular opacities as one of the complications in pregnant

FIG. 3.—Profile view of slit-lamp picture of Case 2, drawn in April 1933.

women with tetany by Meinert (1887) and many others ; (2) pregnancy in rachitic women complicated by tetany cataract, Janáček (1920) ; (3) cataracts in a rachitic woman suffering from convulsions. All of these are possibly of the same type as those we are discussing and of which details are given in the Table.

It will be noted that in some cases the blood-calcium is only slightly below normal, whilst the blood-phosphorus is extremely low. The density of the lenticular opacities varies considerably. In its early stage it is always mild. In these cases it can only be detected by means of the slit-lamp. It is composed of very fine, dust-like opacities in the form of an opaque zone situated right beneath the capsule of the lens. As the disease progresses, the opacities get bigger and extend towards the cortex, with at the same time some water slits. The diagnosis of cataract can then be made with the naked eye. In the course of time the cataract will undoubtedly become ripe, although it runs a slow course, as is evidenced by the last two cases in our list, which came to the eye service direct. It is therefore obvious that any middle-aged or young woman in whom this form of cataract is found should be carefully examined for adult rickets, before a diagnosis of complicated or presenile cataract is made. Under appropriate treatment these cataracts undoubtedly improve, but do not disappear.

CATARACT IN OSTEOMALACIA

No.	Age	Present condition	Past history	Blood chemistry Serum mgm. %	Vision	Examination under the slit-lamp
1	24	8 months' pregnancy. Blurring of vision. Tetany. X-ray: marked osteomalacia. Para III.	Symptoms of osteomalacia 6 years.	Ca 4·65 P 3·15	R.E. $\frac{6}{18}$; corrected $\frac{6}{24}$; J.4 L.E. $\frac{6}{36}$; corrected $\frac{6}{24}$; J.3	R.E.: Lenticular opacities either in the form of spokes or irregular patches. Confined to the anterior subcapsular layers of the lens. L.E. the same.
2	25	Pregnancy 6 months. Tetany. No complaint of vision. X-ray: mild osteomalacia. Para I; Grav. III.	History of tetany occasionally in last 5 years.	Ca 3·5 P 2·2	R.E. $\frac{6}{6}$; J.1 L.E. $\frac{6}{6}$; J.1	R.E.: Irregular lenticular opacities behind the capsule in the form of short spokes and irregular patches. L.E.: In addition dot-shaped opacities. In front of posterior capsule a number of dot and line-shaped opacities. (See illustrations.)
3	28	Pain in the back and legs. Osteomalacia marked. Could not walk without help. No complaint of vision. X-ray: marked osteomalacia. Para II.	Mild symptoms of osteomalacia 7 years before in first pregnancy. Worse in 2nd pregnancy four years ago. Trouble gradually increasing. No history of tetany.	Ca 9·9 P 2·6	R.E. $\frac{6}{18}$; J.2 L.E. $\frac{6}{18}$; J.2 With difficulty.	R.E.: A narrow opaque zone beneath the capsule of the lens. Lenticular opacities in the shape of fine dot-like opacities near the anterior and posterior capsule. L.E.: The same.
4	30	Pregnancy at term. Some blurring of vision. Fractures of left ulna and pubic bones. X-ray: marked osteomalacia. Para I.	History of late rickets, fractures and symptoms of osteomalacia. Occasional mild tetany.	Ca 7·8 P 2·36	R.E. $\frac{6}{10}$; J.4 L.E. $\frac{6}{10}$; J.4	R.E.: An opaque zone extending from the subcapsular layers almost to the anterior and posterior sutures of the lens. Within the opaque zone very fine dust-like opacities are found. The innermost portion and the nucleus of the lens are entirely free from opacities save for some very fine opacities in the centre of the lens.
5	29	Moderate osteomalacia with early deformity of pelvis. No complaint of vision. Para I.	Treated for rickets at the age of 16. No history of tetany.	Ca 7·5 P 1·54	R.E. $\frac{6}{6}$; J.1 L.E. $\frac{6}{6}$; J.1	Both anterior and posterior subcapsular layers of the lens are hazy but without definite opacities.
6	30	Back and bone pain. Had been treated for osteomalacia. X-ray: marked osteomalacia. No complaint of vision. Para III.	Started after the delivery of the first child. Progressively worse, in bed a year. After treatment could walk about. No history of tetany.	Ca 7·99 P 2·20	R.E. $\frac{6}{9}$; J.1 L.E. $\frac{6}{9}$; J.1 With difficulty.	Very fine and few subcapsular lenticular opacities more numerous near the posterior capsule than near the anterior one. The cortex and nucleus remain intact.
7	29	Pregnant 8 months. General back and thigh pain. Difficulty in walking. No complaint of vision. X-ray: marked osteomalacia.	History of mild aching for 8 years. Disability gradually increasing. No history of tetany.	Ca 7·99 P 2·22	R.E. $\frac{6}{9}$; J.1 L.E. $\frac{6}{9}$; J.1	Numerous fine dust-like opacities are found under the epithelial layers both anteriorly and posteriorly of the lens. There are also fine dust-like opacities in the cortex which are bluish in colour.
8	26	Pregnancy at term.	Backache and pain in	Ca 8·4	Normal	Early subcapsular cataract with numerous fine

8	26	Pregnancy at term. General pain in the back and legs. Para IV. X-ray: moderate osteomalacia, esp. chest and pelvis. No complaint of vision.	Backache and pain in the legs since the last pregnancy. No history of tetany.	Ca 8·4 P 2·5	Normal.	Early subcapsular cataract with numerous fine dust-like opacities and water slits scattered within the subcapsular zone and the very anterior portion of the cortex. Both anterior and posterior sutures are found also to be slightly opaque. Very fine opacities are found in the nucleus.
9	31	Pregnancy at term. Pain in the back and legs. Para II. X-ray: mild osteomalacia. No complaint of vision.	Two years before admitted with tetany in labour; craniotomy done. Disease only partially treated.	Ca 6·98 P 2·00	R.E. $\frac{6}{6}$ plus L.E. $\frac{6}{6}$ plus	Numerous dust-like lenticular opacities in the subcapsular layers of the lens; in between them there are a number of water slits.
10	41	Pregnancy at 8 mths. In labour. Backache. Para III. X-ray: marked osteomalacia. No complaint of vision.	Backache and pain in limbs following the two previous deliveries 13 and 11 years ago. Numbness in legs occasionally. No definite tetany.	Ca 5·55 P 1·43	R.E. $\frac{6}{9}$; J.2 with difficulty L.E. $\frac{6}{9}$; J.2 after correction	Fine dust-like opacities are found in the subcapsular layers both anteriorly and posteriorly. The cortex and the nucleus remain intact.
11	40	Tetany. Para II. Prolonged lactation. X-ray: mild osteoporosis, undoubtedly mild osteomalacia. No complaint of vision.	Short history mainly of tetany. Deficiency diet.	Ca 6·50 (P not recorded)	Not noted	Lenticular opacities in the cortical layer more pronounced towards the lens capsule anteriorly and posteriorly. Some dust-like opacities are seen in the periphery of the cortex. A few feather-like opacities are seen near to the equator, and close to the capsule of the lens.
12	34	Reduction of vision without apparent cause. X-ray: mild osteomalacia. Para V (3 singles, 1 twin, 1 triplet).	Occasional tetany since the last childbirth about four yrs. before. Deformity of spine. Deficiency diet. History of defect of vision for one year.	Ca 5·06 P 3·06	R.E.: Hand movement at 1 metre, light perception good in all directions. L.E. $\frac{6}{60}$; J.7	R.E.: Lens entirely opaque. L.E.: Lens opaque in the central part more than in the periphery.
13	40	Back and thigh pain. Deformity of back. Blurring of vision. Para V. X-ray: marked osteomalacia.	After the birth of the third child in 1927 pain in back and thighs. Worse after the fourth child. Deformity, gradually increasing. Blurring of vision began $1\frac{1}{2}$ years ago.	Ca 9·2 P 4·4	R.E.: Hand movement at 30 cm. L.E.: Counting fingers at 20 cm.	Rt. lens entirely opaque with a greyish-white colour. Left lens, opacities in the subcapsular space and the cortex are more or less in the form of radiating patches. In the middle portion of the lens there are several irregular light-grey hard lumps. Behind the cortex the whole lens is almost entirely opaque, except for an irregular dark space in the centre. The opacities are greyish-white with a dark bluish tint.

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Section of Obstetrics and Gynæcology

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Clinical Study of 40 Consecutive Cases of Extra-Uterine Pregnancy

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THE following is an analysis of 40 cases of extra-uterine pregnancy which have been under my care during, approximately, the last three years. Thirty-three of these were seen and treated at the London County Council Hospitals to which I have been attached as part-time consultant and it is with the kind consent of Dr. Allen Daley, the principal medical officer, that I include them in my review. Five cases came under my care at the Samaritan Hospital and two are from private practice.

My analysis is divided into four headings : (1) Diagnosis, signs and symptoms. (2) Pathology. (3) Treatment. (4) Cases of unusual interest.

(1) DIAGNOSIS

I have been guilty during the time these cases were being collected, of opening six abdomens on my own erroneous diagnosis of extra-uterine pregnancy. In four of these, acute salpingitis was found ; in one a threatened miscarriage for which the treatment of laparotomy was successful in averting the threat, and in the last case all the abdominal viscera were normal and I had to wait two days for the appearance of vesicles typical of herpes zoster.

Of my 40 cases, 36 came under my care with some sort of diagnosis attached and these included 4 sent on to me from other hospitals. Of these 36 the diagnosis was correct in 7 and wrong in 29. In 12 of the latter no mention of any part of the genital tract was made, the diagnosis being abdominal pain (5 cases), appendicitis (3 cases), perforated gastric ulcer (1 case), acute intestinal obstruction (1 case), food poisoning (1 case) and internal hæmorrhage (1 case). Of the remaining 17, 7 were labelled miscarriage and 10 other conditions of the genital organs such as menorrhagia or salpingitis. It might be said that these diagnoses were merely labels to expedite admission to hospital, but this object would be better served by the correct diagnosis, and this reason does not account for the four patients sent on from other hospitals. I suspect other people have as great difficulty in making a diagnosis as I have myself. One explanation of failure in diagnosis is the rarity of extra-uterine pregnancy compared with salpingitis and miscarriage for which it is commonly mistaken. My own incidence of cases during the three years under review averaged one every four weeks. This incidence was not uniform but obeyed the well-known clinical rule that rare cases always occur in threes. It must be an unusual event in the life of a

general practitioner to meet these cases, and every credit is due to those who make a correct diagnosis and every excuse to those who fail.

Another important factor in mistaken diagnosis is the sign of amenorrhœa. It is reasonable to assume that some of the early signs of pregnancy would be present whether the pregnancy was intra- or extra-uterine, and amenorrhœa is the most definite and easily determined of these signs. However in 15 out of the 37 cases in which the menstrual history was noted, amenorrhœa could not be established as a sign. In one of these 15 there was not time for menstrual irregularity, rupture of the tube and death occurring within three weeks of the last menstrual period. In 14 cases the last period occurred at the expected time and in all these the punctuality of the period obscures the diagnosis. Only two of the 14 were correctly diagnosed before admission to hospital. Although the menstrual history may show a misleading regularity in time of onset it is of value in other respects, for all these patients had bleeding excessive either in quantity or duration or both, and this menorrhagia becomes of importance when amenorrhœa fails to occur. In no case was the last bleeding normal in all respects, excepting the one who died before menstrual irregularity had time to occur. In 12 of the 14 cases without amenorrhœa the diagnosis before admission to hospital was so wrong as to show that the possibility of any kind of pregnancy had not been considered—not even miscarriage. Outside diagnoses were provided in 20 cases where amenorrhœa had occurred, and in more than half some sort of pregnancy was envisaged for 5 were correctly called ectopics and 7 miscarriages. It emerges that while amenorrhœa is a sign of great help, extra-uterine pregnancy must at times be diagnosed when this sign is absent. I have not found enlargement of the uterus a sign of much value even in nulliparous patients, and it is difficult to make out on account of tenderness. The biological test for anterior pituitary-like hormone in the urine requires time and I have several times found it negative in cases of extra-uterine pregnancy where a positive result would have been of the utmost value. In many cases these difficulties in the early signs of pregnancy constitute the first impediment to a correct diagnosis.

Apart from this question the diagnostic problem in extra-uterine pregnancy presents itself clinically in two forms—the acute and the subacute case. I had 19 acute cases with 3 correct outside diagnoses and 21 subacute cases with 4 correct diagnoses. Of the 19 acute cases who had large extravasation of blood throughout the abdominal cavity 10 had clear unmistakable signs of hæmorrhage such as history of repeated fainting, extreme pallor, rapid breathing and thin, quick and sometimes uncountable pulse. The other 9 cases had not developed such signs although the quantity of blood found seemed just as great. In 21 subacute cases the amount of blood in the peritoneal cavity was small and the sign of acute anæmia was of course absent.

The symptom of pain.—Complaint of pain is probably always made at some time in the history of the patient but not always is it made when she is examined later at hospital and in 13 of my cases it was then absent or trivial. When present, abdominal pain was complained of either all over or in the lower abdomen or limited to the iliac fossa of the affected side. These sites for pain are of little help for they are common to many kinds of abdominal disease. In one case the pain was epigastric and accompanied by nausea and marked signs of internal hæmorrhage ; the last menstrual period had started at the expected time and the patient was referred to me only because it had continued for three weeks. I decided in favour of ruptured extra-uterine pregnancy because of severe pain in both shoulders and tenderness on moving the uterus. That the case should have been admitted as one of perforated gastric ulcer was almost inevitable. Abdominal pain by itself is of small value in the differential diagnosis.

Shoulder pain was present in 7 of the 19 acute cases and in none of the subacute ones. In several it was the main symptom and when present it is to be relied on as a most important sign. I find myself at variance with no less an authority than Bethel Solomons in attaching importance to shoulder pain. In his paper at Amsterdam in May 1938 [1] he considers it of little importance. I feel that shoulder pain in a woman suffering from an acute abdomen is pathognomonic of extra-uterine pregnancy. I will cite one case, not included in this series, which I saw at Charing Cross Hospital when I worked with John Bright Banister ten years ago. Shoulder pain was so severe as to make the patient cry out, and was incomparably greater than any of the abdominal symptoms. She had

[1] *J. Obst. & Gynæc. Brit. Emp.*, **45**, 644.

been treated at home for rheumatism and she stated that the rheumatism was so severe on several occasions as to make her faint repeatedly.

Peculiar and misleading sites for the predominating pain were found in four cases. In two it was situated over the sacrum and in one it was most intense in the region of the anus. In the other it was felt only when the bowels moved.

The sign of tenderness.—Tenderness on deep pressure is in my experience always found over the affected tube but it does not help much in the differential diagnosis from appendicitis or acute salpingitis.

The sign of rigidity.—It is surprising that in both acute and subacute cases rigidity is unusual. In only 3 of the 21 subacute cases was involuntary rigidity present and the same number in the 19 acute cases. In 7 of the acute cases palpation, and indeed inspection, revealed a distinct tumidity and distension of the abdomen due to the large amount of blood in the peritoneal cavity.

Vaginal examination.—This may show a general tenderness without a definable mass and this was found in 7 of my 19 acute cases ; the sign gives no differentiation from acute salpingitis. The sign of sharp tenderness on moving the cervix with one finger is in my experience of great value. The movement of the cervix need not be great and no pressure should be made upwards into the fornices, but the patient responds by a sharp intake of the breath, a throwing back of the head and a sudden straightening of the spine and legs. In my 21 subacute cases this phenomenon was present in 5 and in 9 of the 19 acute cases.

Palpation.—In 18 of 21 subacute cases a tender mass could be identified in either a lateral fornix or in the pouch of Douglas. In the acute group a tender mass was felt in 5 only.

Differential Diagnosis

Considering the wide variety of diagnosis made by other observers in this series, ranging from none at all to influenza, poisoning from tinned salmon, intestinal obstruction and at times to the correct diagnosis, the subject is undoubtedly a difficult one ; especially since the symptom of pain may vary in site from anus to shoulder. I have found the greatest trouble in some cases in distinguishing between extra-uterine pregnancy and acute appendicitis, acute salpingitis and miscarriage. The mistake of appendicitis is not as a rule fatal as operation is usually performed early. It is only in the acute forms of the two diseases that confusion is likely to arise and I have not yet met an extra-uterine pregnancy starting with peri-umbilical pain and vomiting.

Acute salpingitis presents a real difficulty for here the treatment is not surgical. If the diagnosis is not possible at once, then it will emerge as a result of the failure of conservative treatment. I would suggest that an acute salpingitis which gets worse in spite of four days' efficient medical treatment, is likely to be an ectopic pregnancy. Six of my 21 subacute cases were kept waiting at least three days on my diagnosis of acute salpingitis. Two of these had been sent to me from teaching hospitals with this diagnosis and I found great difficulty in bringing myself to alter such an *ex cathedra* pronouncement. The differential diagnosis from miscarriage seems to depend on the very different kind of pain and tenderness in extra-uterine pregnancy and on the discovery of a mass distinct from the uterine body. It is in these cases that examination under anæsthesia is valuable.

(2) Pathology

On the whole the possible predisposing pathological conditions were unconvincing. There were 14 nulliparous patients of whom two had had gonorrhœa and one a pelvic peritonitis. The other 11 had no history of probable tubal disease and showed no old-standing gross pathology at operation. Of 26 parous patients, 20 had last had a child and 6 a miscarriage and the average time since the event was six years, which corresponds with the usual figure. In one case the tubal abnormality was probably congenital for the opposite ovary was absent and the tube rudimentary. In six cases a previous pelvic operation had been performed. In two it was a previous ectopic pregnancy. In another, suspension of an ovary and division of pelvic adhesions had been done. It seems probable that in each of these the two operations had a common antecedent inflammatory cause. A fourth had had a fibroid removed to allow pregnancy to occur. The fifth had had

Cæsarean section for her first baby two years previously. The last seems to have had an unnecessary laparotomy, which she had been told was a mistake, while pregnant with her last child four years previously. In these three, previous surgery seems to have been a predisposing factor. I was surprised that no patient gave a history of insufflation of the tubes for I suspect this operation of being almost as fertile of extra- as of intra-uterine pregnancies. The conditions found at operation in the 21 subacute cases were 13 tubal abortions, 5 tubal moles, and 3 tubal ruptures. In the acute cases there were 11 tubal abortions, 7 ruptures and 1 mole. In this last case the tube was not ruptured and no bleeding was taking place from the abdominal ostium but the tube was bleeding from a superficial vascular "ulcer" evidently caused by chorionic villi which had grown through the tube wall. The whole abdomen was full of blood. I was much impressed with how often the condition of tubal abortion is accompanied by a hæmorrhage of the first magnitude. More than half of my acute cases were tubal abortions and these showed as great a degree of exsanguination as the patients with tubal rupture.

(3) Treatment

There is now little difference of opinion about the urgency of operation in all cases. I noted, however, in two of the five tubal moles of the subacute group, that there was no blood in the peritoneal cavity. In both the lump formed by the mole was small and discrete and operation was undertaken after some delay, mainly on the symptom of marked tenderness. One is tempted to speculate that these two moles might have become organized without the occurrence of any further hæmorrhage.

In operative technique I take trouble to preserve ovaries and to wipe their surface free of adherent blood-clot. Twice an attempt has been made to repair and preserve the affected tube but I had little hope of either of them functioning again.

Except in patients seriously ill the tube of the opposite side is inspected and removed if diseased.

Blood transfusion.—It is surprising from what profound anæmia a patient may recover when blood is not available, but I am convinced of the value of transfusion in the worst cases. Transfusion of blood was employed at the time of operation in 12 of my 19 acute cases. Seven of these were tubal abortions, four were tubal ruptures and one was the mole with erosion by chorionic villi. In nine cases auto-transfusion was done and in three blood was taken from a donor. The procedure which seems to work best is to give donor's blood on the operating table and with everything prepared for laparotomy. When the patient's colour, pulse and blood-pressure have improved, as they will temporarily, the operation is begun. It may be necessary to wait twenty minutes or half an hour for the optimum moment to arrive. Within a few minutes after beginning, with the help of an electric sucker, several pints of the patient's blood can be ready for continuing the transfusion. The first pint of blood can be given within half an hour and the transfusion then continued at the rate of a drop a second or slower.

It seems important for quick convalescence to remove the large clots to be found in the pouch of Douglas and in the kidney regions. The fluid blood not removed for auto-transfusion is left for its plasma to be re-absorbed.

(4) Cases of Unusual Interest

Under this heading come the six cases already noted in which previous surgery may have had something to do with the ætiology of the extra-uterine pregnancy.

The case mentioned with profuse hæmorrhage due to erosion by chorionic villi, without either tubal abortion or rupture, refutes the idea that any case might be left without operation.

There was one patient with a left tubal mole and a right hæmatosalpinx. This was probably a double ectopic but I could not have the hæmatosalpinx sectioned as the tube was preserved to give the patient a chance of fertility.

In one case a typical rupture had occurred at the distended ampullary end of the tube, the abdominal ostium of which was closely sealed off. In one case the influence of gonorrhœa was clear. The patient was one of the three in my series who were unmarried. Her activities had been restricted in a home under a magistrate's order where treatment

for acute gonorrhœa had resulted in a cure according to all the tests for cure. In view of this and her marked docility of nature she was allowed out for an afternoon to have tea with her parents. During this social event the seed was sown which in a few weeks led to her rapid removal to my ward.

Two deaths occurred. Both these patients were acutely ill and both died on the operating table ; both had small ruptures of the isthmial part of the tube and owing to various delays both had been kept for many hours, 11 and 18, in a state of profound collapse. Judging from other cases in which collapse was equally great but of shorter duration, and who almost died but ultimately recovered, it seems that duration of collapse is of the first importance and that if it lasts beyond a certain time—probably about eight hours—there is no possibility of recovery whatever treatment is employed.

In one of these cases direct cardiac massage was performed. The patient had received blood transfusion, the operation was completed and she was being bandaged when pulse and respiration stopped and she apparently died. Intracardiac injections of coramine and adrenaline were without effect so the abdomen was opened again in the left hypochondrium. The fibres of the left cupola of the diaphragm were split and the pericardial cavity penetrated with two fingers which were passed behind the heart. Gentle massage resulted in strong contractions of the heart within three minutes. Præcordial pulsation became marked, the radial pulse could be counted and the patient's colour became bright red. There was, however, no spontaneous attempt at respiration and after ten minutes the heart began to beat feebly and finally stopped. A second massage of the heart was successful but for a shorter time and thereafter no response was obtained.

DISCUSSION ON THE PATHOLOGY OF CERVICITIS

Mr. Aleck Bourne : During the course of histological work on the cervix while engaged in investigating the therapeutic action of zinc chloride, Dr. Bond and I were impressed by the comparative absence of the true signs of inflammation in a large number of cervices examined. The cervix had been amputated for leucorrhœa, and, in many cases, exhibited very advanced macroscopic signs of what is commonly called " cervicitis ", usually ascribed to the effects of chronic inflammation. The symptom regarded as typical of cervical inflammation is leucorrhœa, while the signs are erosion, enlargement, eversion and follicles. It is obvious that there are a number of cases of true cervicitis, as for example those of gonorrhœa and an occasional pyogenic infection following labour or abortion, but if these are excluded, the majority are found to show very little beyond hypertrophy of all the tissue elements, and increased activity of the gland cells. Many erosions, even, show only the slightest and most superficial inflammatory reaction, such as might be caused by contact of columnar epithelium with the acid medium of the vagina.

Bacteriological examination of the cervical canal and the mucus expressed from the deep glands also finds little evidence of active infection, always excepting gonorrhœa.

Even in the worst cases of leucorrhœa, cultures of true pathogens can rarely be grown, and frequently the canal is entirely sterile. The occasional occurrence of a colony or more of Döderlein's bacillus shows how easily the canal may be contaminated by the vaginal discharge however carefully the swab is passed through the os. Moreover, if the contents of a Naboth's follicle are cultured both aerobically and anaerobically, the result is usually a sterile plate. The preservation of the cervical canal from infection depends on a mechanism with which we are not yet entirely familiar, but which must be remarkably efficient. For example, in many cases of vaginitis due to trichomonas and a pyogenic infection, it is usual to find the cervical canal sterile, even though the contents of the vagina at the very margin of the external os are frankly purulent. In the ordinary case of leucorrhœa commonly labelled " cervicitis ", we have actual difficulty in demonstrating the effects of inflammation in the tissues, or infection in the glands and mucus of the canal.

If, now, the actual discharge as found in the vagina is examined by film and culture and acid reaction, it is surprising to find how many of them show little or no elements of pus or pyogenic organisms, but, instead, large masses of squamous cells, Döderlein's bacilli, and a few indeterminate organisms which seldom appear on the culture plate.

The pH varies from 4 to 5. In others, taken from a vagina showing a little redness or actual vaginitis, the discharge of a pH from 5 to 7 may have all the characters of true pus, but such examples are uncommon during the childbearing period except from cases of gonorrhœa or trichomoniasis.

If the origin of leucorrhœal discharges shows little or no signs of inflammation, so also does the actual discharge itself, even when taken from the vagina.

While the state of cervical infection and inflammation may be postulated in married or parous women, this cannot be advanced to account for the often profuse leucorrhœa of young virgins. The discharge of these patients may be as copious as that found in any other patient and associated with a large red erosion, but in these women it is very highly acid and shows no trace of infection.

There is other evidence also which I have no time to describe in detail, strongly suggesting that we must discard the term "cervicitis" for the majority of cases of leucorrhœa and adopt a new idea based upon an endocrine pathology.

There is a condition of the uterine body, generally recognized as the result of an imbalance of the ovarian hormones. It is not inflammatory, but is associated with hypertrophy and menstrual excess and irregularity. The name—metropathia—suggests the name "trachelopathia" for the analogous condition of the cervix. We know that the endometrium is closely controlled by the follicle-luteal mechanism, and we also recognize now that the cervical mucosa is also subject to certain rhythmic changes during the menstrual month. We submit, therefore, that an aberration of the endocrine secretion or of its activation of receptors in the local tissues can be and is responsible firstly for the disturbance of function of the cervical glands, and later for an alteration in structure of the cervical tissues.

It is important to reconsider the histology and pathology of the non-malignant cervix and to re-examine its relationship to the hormonal activity of the ovary.

Dr. L. T. Bond: The textbooks teach us that chronic cervical discharge is the result of infection either by the gonococcus or by pathogenic organisms which gain entrance to the cervical tissues when they are traumatized during labour, and that such infection frequently becomes established "in the deepest recesses of the compound racemose glands lining the canal" where it remains for years as a focus of irritation causing hypertrophy and excessive activity of the cervical glands.

Now in studying the histology of chronic cervicitis I have been struck with the absence of any evidence of inflammation around the fundi of the cervical glands in many of the cases, and in the histological examination of well over a hundred cervices in the last few years I have been further impressed with the apparent lack of correlation between cervical discharge and microscopical evidence of infection in the canal.

In order to make the general topography of cervical sections and the distribution of inflammation clearer, I have made a number of diagrams using a 3-inch objective and tracing the outlines of the glands, &c., on paper; by this means a plan of the cervical tissues is obtained under a magnification of 7 diameters, which is considerably less than the usual low power and therefore includes the whole transverse section of the canal in one field; different types of shading are used to distinguish the two types of epithelium, and areas of acute or chronic inflammation.

Such a diagram from a normal cervix shows, in the transverse (fig. 1b), an average gland layer, and in the longitudinal (fig. 1a) the squamous epithelium extending to just inside the external os, and a small collection of inflammatory cells at the epithelial frontier and in the papillæ of the canal which seems almost universal, even in normal cervices.

On the other hand, in a corresponding diagram from a case of chronic cervicitis, there is enormous hypertrophy of the gland layer in the transverse (fig. 2b) without any sign whatever of inflammation around the canal, while in the longitudinal (fig. 2a) the gland layer extends on to the portio, where there is an erosion in which the superficial layers, only, show chronic inflammation and this ceases abruptly at the external os.

This picture makes it difficult to believe that infection can be present deep in the glands of the canal, since, were pathogenic organisms there, they must surely give some evidence of their presence in the shape of an inflammatory reaction in the adjacent tissues; on the

other hand, the very superficial distribution of that inflammation which is present, i.e. in the erosion, cannot but suggest that its cause originates on the surface, and not from the fundi of the glands, and that the irritant must exist in the vagina since it appears not to be effective within the canal.

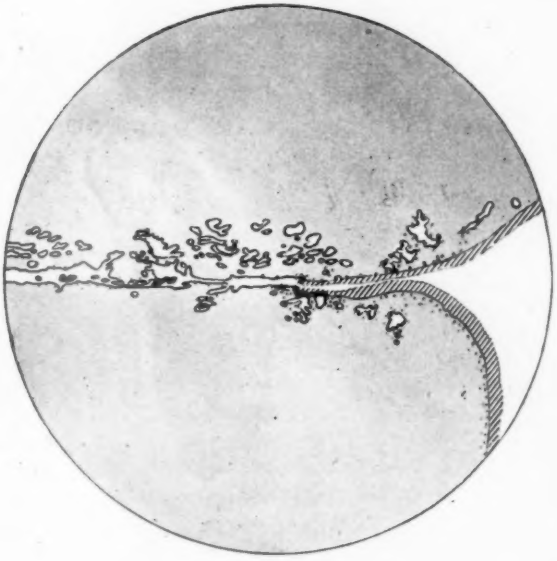

FIG. 1a.

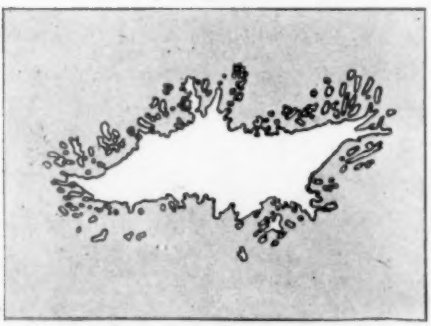

FIG. 1b.

Case 31.—Aged 39. Nulliparous. Operation for fibroids. No leucorrhœa.

These considerations have led us to wonder whether, in many cases of cervicitis, there is not some factor other than bacterial infection responsible for the hypertrophy and activity of the gland layer, and, in view of the undoubted influence of ovarian hormones

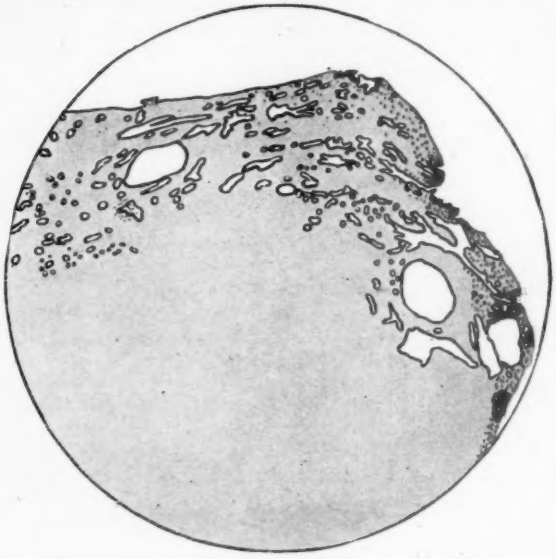

FIG. 2a.

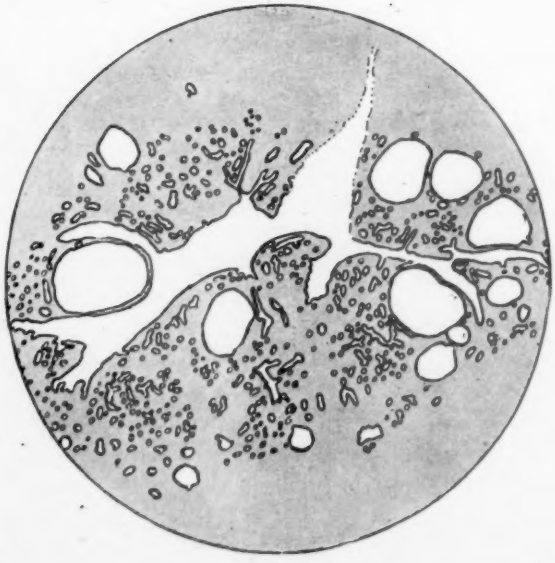

FIG. 2b.

Case 14.—Aged 47. Seven children, last one ten years ago. Operation for cystocele and chronic cervicitis. Some thick, viscid leucorrhœa. Cervix—very large erosion.

on other parts of the genital tract, it seems reasonable to suggest some disordered balance of these hormones, such as excessive production of œstrin.

It is possible that the inflammation localized in the erosion, once it is present, may play

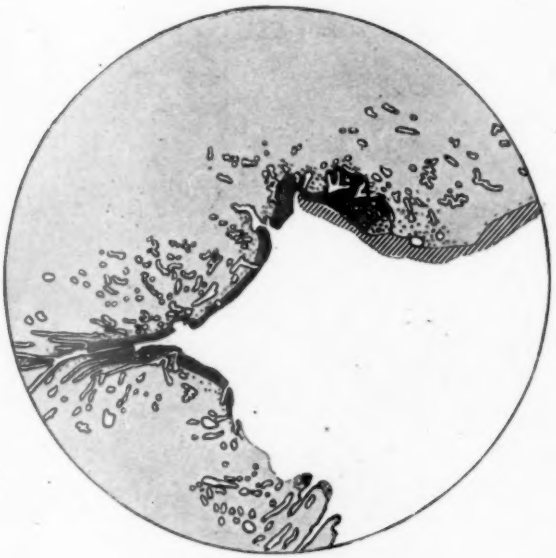

FIG. 3a.

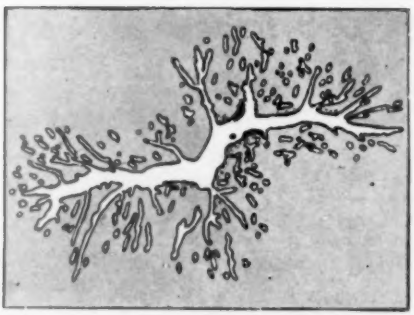

FIG. 3b.

Case 112.—Aged 42. One child, nine years ago. Operation for prolapse. Leucorrhœa—slight yellowish. Cervix macroscopically lacerated, with marked eversion.

a small part in establishing a vicious circle, but it does not seem extensive enough to account for such a profound anatomical and physiological upset as that which occurs in the glands in chronic cervicitis ; may it not be that the glandular hypertrophy comes first,

as a result of disordered hormone balance, and that this leads to spread of the columnar epithelium and gland layer on to the portio, where the intensely acid contents of the vagina cause loss of epithelial covering and superficial inflammation as a result of chemical, not bacterial, irritation of the exposed tissues.

FIG. 4.

Case 124.—Aged 22. Virgo intacta. Biopsy of erosion: Thick, mucoid excessive discharge, pH 3·5. Culture: *B. döderlein* and anaerobic diphtheroids. Cervix: Circular, granular erosion.

FIGS. 1—4 (Diagrams of cervix sections × 5·25 diameters).

Key to shading:—

The fibromuscular tissue of the cervix.

Chronic inflammation.

Acute inflammation.

Squamous epithelium.

Where the outlines of the glands are a single black line this always represents columnar epithelium.

This may also be the explanation of the small zone of inflammation we have seen at the epithelial frontier in normal cervices, as the vaginal acidity probably extends for a short distance inside the external os.

It is, of course, not true to say that cervical discharge is never due to infection ; gonococcal cervicitis provides a definite instance of this, but in that case we are dealing with a truly pathogenic organism, whereas bacteria which have been isolated from time to time in non-gonococcal cervicitis have often been of very doubtful pathogenicity.

The discharge which accompanies eversion is probably due to the irritation caused by exposure of a large part of the lining of the canal to the vaginal contents, and the consequent inflammation of a large area (fig. 3a), but this is not necessarily accompanied by glandular hypertrophy such as is seen in so-called cervicitis (fig. 3b).

Microscopical evidence of inflammation within the cervical canal is seen in a variety of conditions, especially infections of other parts of the genital tract, e.g. salpingitis and ovarian abscess, and sometimes accompanying urinary infections ; it is also seen in some post-menopausal cervices, but in none of these conditions is it necessarily accompanied by cervical discharge, such as one would be led to expect on the inflammatory theory of cervicitis.

A form of cervical leucorrhœa the ætiology of which seems to remain obscure is that which accompanies the congenital or virginal erosion ; in the majority of these cases infection can be ruled out completely, and yet the discharge may be very profuse ; when an erosion is present it often shows similar superficial inflammation (fig. 4) to cases of cervicitis in older women ; this is confirmatory evidence of the irritant action of the vaginal contents on erosions, since the congenital ones are admittedly of non-infective ætiology.

The condition is called congenital because it resembles the erosion sometimes seen in babies in the first week or two of life ; as Sjövall (1938) has pointed out, the child is, at this stage, still under the influence of maternal œstrin reaching it via the placenta ; when this has been excreted the erosion disappears, and it is not until puberty, when œstrin is once more available, that it is liable to return as a virginal erosion ; if, as appears from this, œstrin is a factor in the production of the admittedly non-infective erosion and leucorrhœa of virgins, it seems reasonable to suggest that it may also play a part in a similar condition in older women.

The cervix has been called the pelvic tonsil, but the term is a most inappropriate one, because, quite apart from the complete histological dissimilarity between the two structures, the crypts of the tonsil are lined by inactive squamous epithelium and afford an ideal breeding ground for bacteria, whereas the cervical glands are lined by columnar epithelium, the mucous secretion from which is probably bactericidal, and constantly tends to wash the organisms out.

I have approached the problem of cervical leucorrhœa mainly from the angle of histological evidence of inflammation, to see whether the use of the term cervicitis, denoting an inflammatory condition, is always justified ; but it has also been approached from the hormonal angle.

Recent research has led to the conclusion, contrary to the views of earlier workers, that the cervix has a definite menstrual cycle, and that it is demonstrably under the influence of ovarian hormones ; Woolner (1938) has correlated it with the endometrial cycle, and has come to the conclusion that many of the histological pictures in the cervix which were previously thought to be inflammatory are, in fact, part of the normal menstrual cycle.

One example of such a picture which we have come across is an accumulation of polymorphonuclear leucocytes which occurs under the cervical lining just before, and during, menstrual flow ; at first sight this might be taken for an intense, acute inflammation, but it is unaccompanied by other signs of inflammation and appears to be part of the physiological cycle.

Woolner suggests that, in view of the undoubted influence of œstrin on the cervical mucosa, the evaluation of increased cervical discharge as an expression of inflammatory involvement requires revision, and that glandular hyperplasia and hypersecretion may be a hormonal phenomenon ; he compares the misinterpretation of inflammatory pictures in the cervix, to similar misinterpretation of normal endometrial phases as endometritis, before Hitschman and Adler's classic work.

I have briefly demonstrated some features in the pathology of cervicitis, and suggest as a hypothesis for discussion that hormonal influence, possibly over-production of œstrin, is a factor, if not the paramount factor, in the causation of many cases of so-called chronic cervicitis, and that genuine bacterial infection is by no means always present in cases of excessive cervical discharge.

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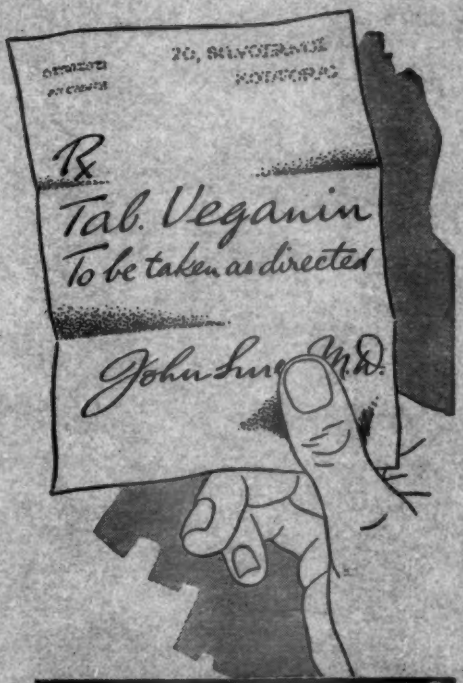

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